

# *Scleromitron diffusum*: A Comprehensive Review of its Botany, Phytochemistry, Pharmacology and Clinical Application

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**Abstract:** *Scleromitron 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:** *Scleromitron diffusum*; phytochemistry; pharmacology; clinical application. ©2025 ACG Publications. All rights reserved.

## 1. Introduction

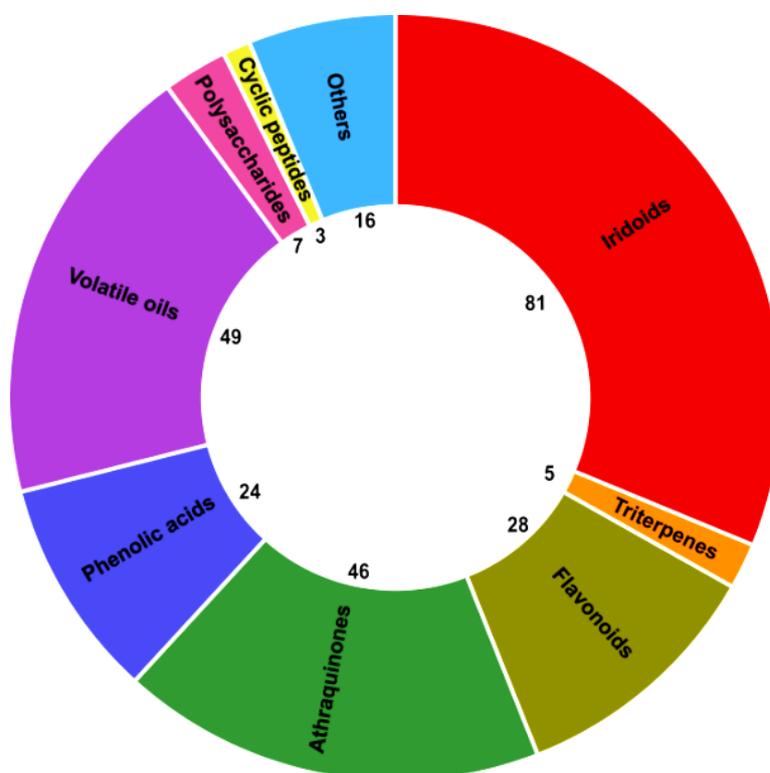
Plants, a precious gift from nature, serve not only as vital food sources but also as essential contributors to drug development [1,2]. As awareness of the therapeutic potential of plants grows, phytotherapy becomes an integral part of modern medical systems [3,4]. In this context, developing

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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]. *Scleromitron 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

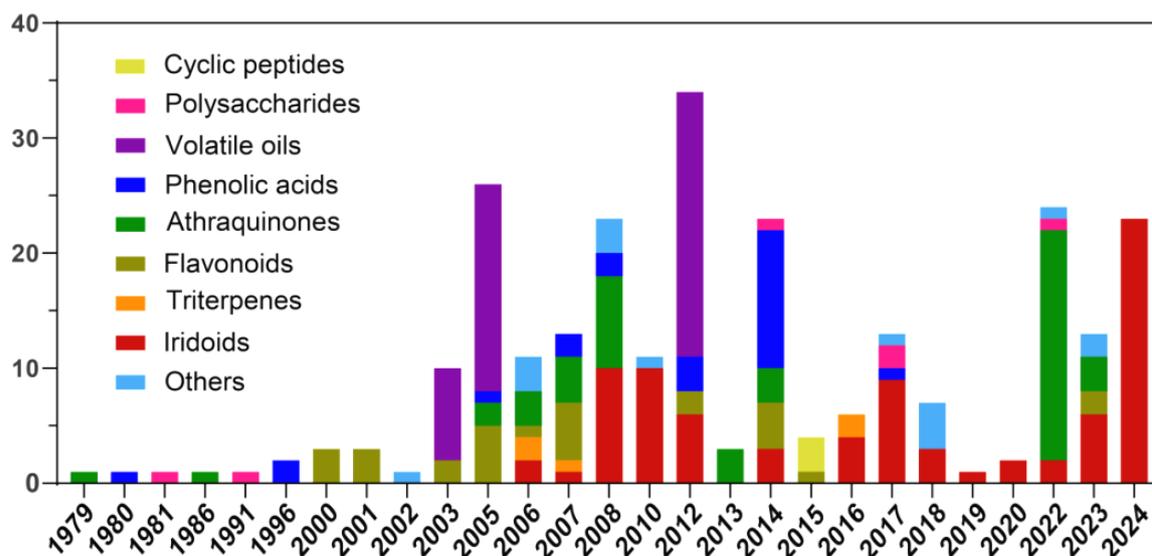


Figure 2. All secondary metabolites by source/year, n = 259

## 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 *Scleromitron 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.

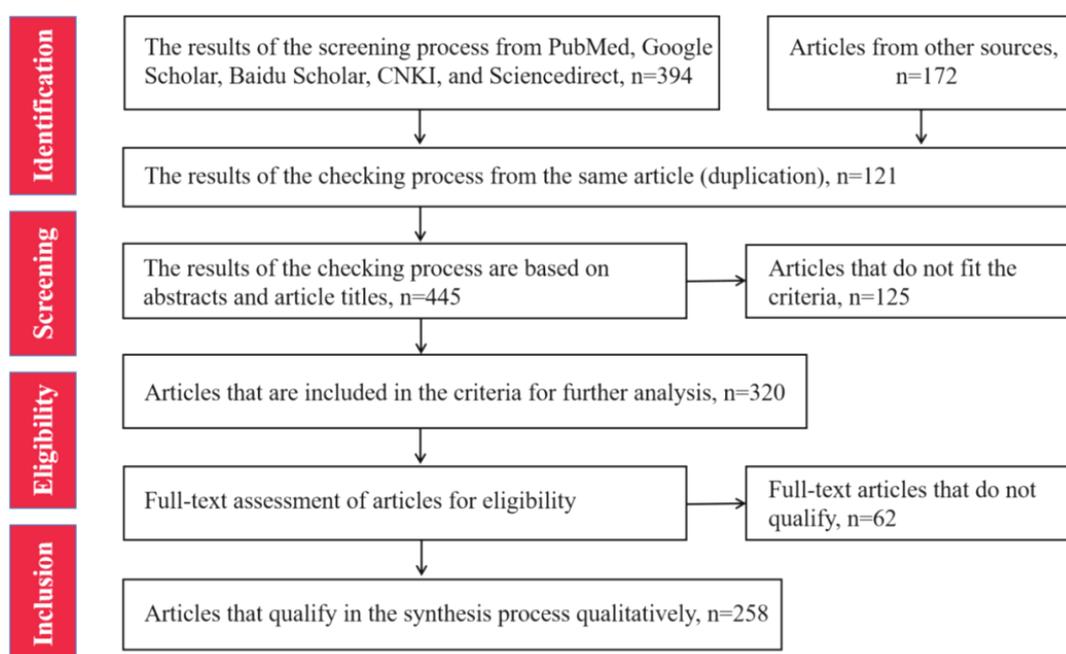
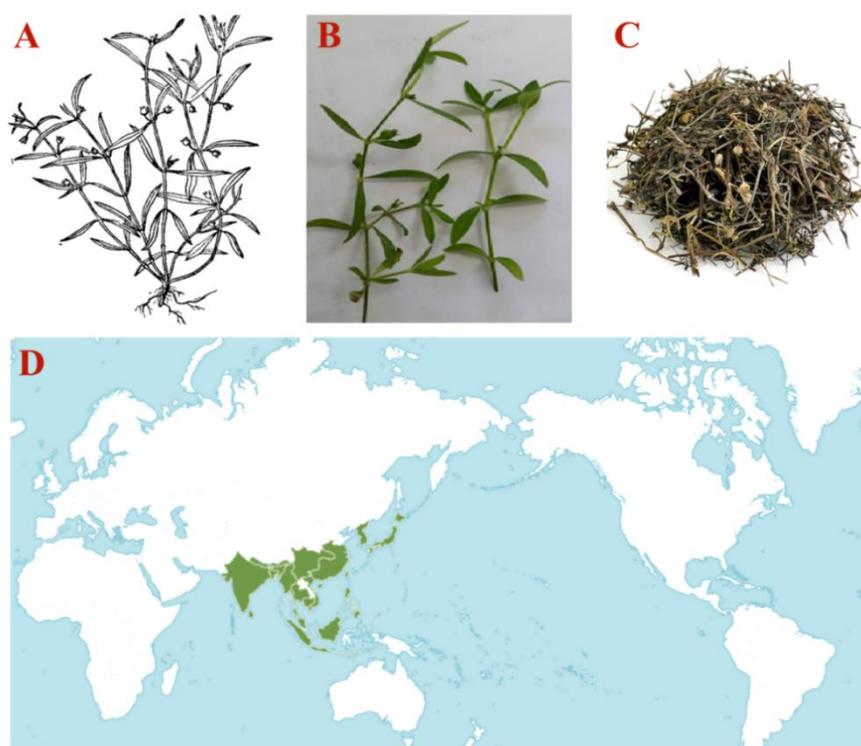


Figure 3. Research data search & selection flow.

### 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) (*Scleromitron 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** anthraquinones (**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.
<b>Iridoids</b>					
1.	geniposidic acid	C <sub>16</sub> H <sub>22</sub> O <sub>10</sub>	374.34	2016	[16]
2.	6-dehydro scandoside	C <sub>16</sub> H <sub>22</sub> O <sub>10</sub>	374.34	2006	[17]
3.	10- <i>O</i> -acetyl geniposidic acid	C <sub>18</sub> H <sub>24</sub> O <sub>11</sub>	416.38	2012	[172]
4.	10-dehydro geniposide	C <sub>17</sub> H <sub>22</sub> O <sub>10</sub>	386.35	2008	[173]
5.	10-dehydro geniposidic acid	C <sub>16</sub> H <sub>20</sub> O <sub>10</sub>	372.33	2006	[17]
6.	deacetyl asperulosidic acid	C <sub>16</sub> H <sub>22</sub> O <sub>11</sub>	390.34	2012	[172, 174]
7.	deacetyl asperulosidic acid methyl ester	C <sub>17</sub> H <sub>24</sub> O <sub>11</sub>	404.37	2008	[172, 173]
8.	6- $\alpha$ -hydro scandoside	C <sub>16</sub> H <sub>22</sub> O <sub>11</sub>	390.34	2008	[175]
9.	6- $\beta$ -hydro scandoside	C <sub>16</sub> H <sub>22</sub> O <sub>11</sub>	390.34	2008	[175]
10.	6- $\alpha$ -hydro scandoside methyl ester	C <sub>17</sub> H <sub>24</sub> O <sub>11</sub>	404.37	2008	[175]
11.	6- $\beta$ -hydro scandoside methyl ester	C <sub>17</sub> H <sub>24</sub> O <sub>11</sub>	404.37	2008	[175]
12.	scandoside methyl ester	C <sub>17</sub> H <sub>24</sub> O <sub>11</sub>	404.37	2010	[33, 174]
13.	asperuloside acid	C <sub>19</sub> H <sub>26</sub> O <sub>12</sub>	446.41	1981	[176]
14.	6- $\alpha$ -hydro-10-acetyl asperuloside acid	C <sub>18</sub> H <sub>24</sub> O <sub>12</sub>	432.38	2008	[175]
15.	6- $\beta$ -hydro-10-acetyl asperuloside acid	C <sub>18</sub> H <sub>24</sub> O <sub>12</sub>	432.38	2008	[175]
16.	asperulosidic acid methyl ester	C <sub>19</sub> H <sub>26</sub> O <sub>12</sub>	446.41	2010	[33]
17.	daphylloside	C <sub>19</sub> H <sub>26</sub> O <sub>12</sub>	446.41	2023	[174]
18.	productasperulosidic acid butyl ester	C <sub>22</sub> H <sub>32</sub> O <sub>12</sub>	488.49	2023	[174]
19.	6- <i>O</i> -methyl deacetyl asperulosidic acid methyl ester	C <sub>18</sub> H <sub>26</sub> O <sub>11</sub>	418.40	2010	[33]
20.	deacetyl-6-ethoxyasperulosidic acid methyl ester	C <sub>19</sub> H <sub>28</sub> O <sub>11</sub>	432.42	2010	[33]
21.	diffusoside A	C <sub>19</sub> H <sub>28</sub> O <sub>11</sub>	432.42	2010	[177]
22.	diffusoside B	C <sub>19</sub> H <sub>28</sub> O <sub>11</sub>	432.42	2010	[177]
23.	diffusoside C	C <sub>20</sub> H <sub>30</sub> O <sub>12</sub>	462.45	2022	[178]
24.	diffusoside D	C <sub>20</sub> H <sub>30</sub> O <sub>12</sub>	462.45	2022	[178]

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

56.	diffusadoid M	C <sub>30</sub> H <sub>34</sub> O <sub>15</sub>	634.59	2024	[123]
57.	diffusadoid N	C <sub>30</sub> H <sub>34</sub> O <sub>15</sub>	634.59	2024	[123]
58.	diffusadoid O	C <sub>29</sub> H <sub>34</sub> O <sub>15</sub>	622.58	2024	[123]
59.	diffusadoid P	C <sub>31</sub> H <sub>36</sub> O <sub>16</sub>	644.61	2024	[123]
60.	11-methoxyviburtinal	C <sub>10</sub> H <sub>8</sub> O <sub>3</sub>	176.17	2017	[32]
61.	monotropein methyl ester	C <sub>17</sub> H <sub>24</sub> O <sub>11</sub>	404.37	2010	[33]
62.	hehycoryside C	C <sub>23</sub> H <sub>26</sub> O <sub>11</sub>	478.45	2014	[182]
63.	10- <i>O</i> -benzoyl scandoside methyl ester	C <sub>24</sub> H <sub>28</sub> O <sub>12</sub>	508.48	2023	[174]
64.	10- <i>O</i> -benzoyl-6'- <i>O</i> - $\alpha$ -L-arabino(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranosylgeniposidic acid	C <sub>28</sub> H <sub>34</sub> O <sub>15</sub>	610.57	2010	[33]
65.	oldenlandoside III	C <sub>34</sub> H <sub>44</sub> O <sub>20</sub>	772.71	2014	[182]
66.	patrinoside	C <sub>21</sub> H <sub>34</sub> O <sub>11</sub>	462.49	2017	[32]
67.	suspensolide F	C <sub>21</sub> H <sub>34</sub> O <sub>12</sub>	478.49	2017	[32]
68.	hedyoiridoidside A	C <sub>21</sub> H <sub>32</sub> O <sub>10</sub>	444.48	2018	[60]
69.	hedyoiridoidside B	C <sub>22</sub> H <sub>38</sub> O <sub>13</sub>	510.53	2018	[60]
70.	15-demethylisoplumieride	C <sub>20</sub> H <sub>26</sub> O <sub>11</sub>	442.42	2017	[32]
71.	shecaoiridoidside B	C <sub>21</sub> H <sub>32</sub> O <sub>13</sub>	492.47	2017	[32]
72.	jatamanin E	C <sub>10</sub> H <sub>14</sub> O <sub>5</sub>	214.22	2017	[32]
73.	shecaoiridoidside A	C <sub>22</sub> H <sub>32</sub> O <sub>12</sub>	488.49	2017	[32]
74.	kanokoside A	C <sub>22</sub> H <sub>34</sub> O <sub>12</sub>	490.50	2017	[32]
75.	hedyoiridoidside C	C <sub>22</sub> H <sub>36</sub> O <sub>10</sub>	460.52	2018	[60]
76.	alpigenoside	C <sub>18</sub> H <sub>28</sub> O <sub>10</sub>	436.41	2012	[172]
77.	4-epiborreriagenin	C <sub>11</sub> H <sub>16</sub> O <sub>4</sub>	212.25	2010	[33]
78.	shecaoiridoidside C	C <sub>23</sub> H <sub>28</sub> O <sub>10</sub>	464.47	2017	[32]
79.	asperuloside	C <sub>18</sub> H <sub>22</sub> O <sub>11</sub>	414.36	2007	[179, 183]
80.	deacetyl asperuloside	C <sub>16</sub> H <sub>20</sub> O <sub>10</sub>	372.33	2012	[172]
81.	diffusadoid Q	C <sub>20</sub> H <sub>24</sub> O <sub>12</sub>	456.40	2024	[123]
<b>Triterpenes</b>					
82.	lupenylacetate	C <sub>32</sub> H <sub>52</sub> O <sub>2</sub>	468.77	2007	[34]
83.	arborinone	C <sub>30</sub> H <sub>48</sub> O	424.71	2016	[16]
84.	isoarborinol	C <sub>30</sub> H <sub>50</sub> O	426.73	2016	[16]
85.	oleanolic acid	C <sub>30</sub> H <sub>48</sub> O <sub>3</sub>	456.71	2006	[17]
86.	ursolic acid	C <sub>30</sub> H <sub>48</sub> O <sub>3</sub>	456.71	2006	[17]
<b>Flavonoids</b>					
87.	amentoflavone	C <sub>30</sub> H <sub>18</sub> O <sub>10</sub>	538.46	2005	[36, 37]
88.	chrysin-6- <i>O</i> -glucosyl-8- <i>O</i> -arabinosyl	C <sub>26</sub> H <sub>28</sub> O <sub>13</sub>	548.50	2014	[182]
89.	chrysin-6- <i>O</i> -arabinosyl-8- <i>O</i> -glucosyl	C <sub>26</sub> H <sub>28</sub> O <sub>13</sub>	548.50	2014	[182]
90.	oroxylin A- <i>O</i> -glucuronic acid	C <sub>22</sub> H <sub>20</sub> O <sub>11</sub>	460.39	2014	[182]
91.	wogonin- <i>O</i> -glucuronic acid	C <sub>22</sub> H <sub>20</sub> O <sub>11</sub>	460.39	2014	[182]
92.	5,7-dihydroxy-3-methoxy flavonol	C <sub>16</sub> H <sub>12</sub> O <sub>6</sub>	300.27	2007	[183]
93.	5,7,4'-trihydroxy flavonol	C <sub>15</sub> H <sub>10</sub> O <sub>6</sub>	286.24	2007	[183]
94.	5-hydroxy-6,7,3',4'-tetramethoxy flavone	C <sub>19</sub> H <sub>18</sub> O <sub>7</sub>	358.35	2007	[34]
95.	quercetin	C <sub>15</sub> H <sub>10</sub> O <sub>7</sub>	302.24	2006	[17, 20, 173]
96.	rutin	C <sub>28</sub> H <sub>32</sub> O <sub>15</sub>	608.55	2007	[18, 172, 184]

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97.	quercetin-3- <i>O</i> - $\beta$ -D-glucopyranside	C <sub>21</sub> H <sub>20</sub> O <sub>12</sub>	464.38	2000	[18, 185, 186]
98.	quercetin-3- <i>O</i> - $\beta$ -D-galactopyranoside	C <sub>21</sub> H <sub>20</sub> O <sub>12</sub>	464.38	2005	[185]
99.	quercetin-3- <i>O</i> -(2- <i>O</i> -glucopyranosyl)- $\beta$ -D-glucopyranside	C <sub>27</sub> H <sub>30</sub> O <sub>17</sub>	626.52	2000	[18, 172, 185, 186]
100.	quercetin-3- <i>O</i> -(2- <i>O</i> -glucopyranosyl)- $\beta$ -D-galactopyranoside	C <sub>27</sub> H <sub>30</sub> O <sub>17</sub>	626.52	2001	[187, 188]
101.	quercetin-3- <i>O</i> -sambubioside	C <sub>26</sub> H <sub>28</sub> O <sub>16</sub>	596.49	2012	[18, 172]
102.	quercetin-3- <i>O</i> -[2- <i>O</i> -(6- <i>O</i> - <i>E</i> -feruloyl)- $\beta$ -D-glucopyranosyl]- $\beta$ -D-galactopyranoside	C <sub>37</sub> H <sub>38</sub> O <sub>20</sub>	802.69	2001	[187, 188]
103.	quercetin-3- <i>O</i> -[2- <i>O</i> -(6- <i>O</i> - <i>E</i> -feruloyl)- $\beta$ -D-glucopyranosyl]- $\beta$ -D-glucopyranoside	C <sub>37</sub> H <sub>38</sub> O <sub>20</sub>	802.69	2003	[18, 172, 187]
104.	quercetin-3- <i>O</i> -[2- <i>O</i> -(6- <i>O</i> - <i>E</i> -sinapoyl)- $\beta$ -D-glucopyranosyl]- $\beta$ -D-glucopyranoside	C <sub>38</sub> H <sub>40</sub> O <sub>21</sub>	832.72	2012	[172]
105.	quercetin-3- <i>O</i> -[2- <i>O</i> -(6- <i>O</i> - <i>E</i> -sinapoyl)- $\beta$ -D-glucopyranosyl]- $\beta$ -D-galactopyranoside	C <sub>38</sub> H <sub>40</sub> O <sub>21</sub>	832.72	2015	[18]
106.	kaempferol	C <sub>15</sub> H <sub>10</sub> O <sub>6</sub>	286.24	2003	[173, 189]
107.	kaempferol-3- <i>O</i> - $\beta$ -D-glucopyranside	C <sub>21</sub> H <sub>20</sub> O <sub>11</sub>	448.38	2005	[185]
108.	kaempferol-3- <i>O</i> - $\beta$ -D-galactopyranoside	C <sub>21</sub> H <sub>20</sub> O <sub>11</sub>	448.38	2005	[185]
109.	kaempferol-3- <i>O</i> -(2- <i>O</i> - $\beta$ -D-glucopyranosyl)- $\beta$ -D-galactopyranoside	C <sub>27</sub> H <sub>30</sub> O <sub>16</sub>	610.52	2001	[18, 187, 188]
110.	kaempferol-3- <i>O</i> -(6- <i>O</i> - $\alpha$ -L-rhamnosyl)- $\beta$ -D-glucopyranside	C <sub>27</sub> H <sub>30</sub> O <sub>15</sub>	594.52	2005	[185]
111.	kaempferol-3- <i>O</i> -[2- <i>O</i> -( <i>E</i> -6- <i>O</i> -feruloyl)- $\beta$ -D-glucopyranosyl]- $\beta$ -D-glucopyranosyl	C <sub>37</sub> H <sub>38</sub> O <sub>19</sub>	786.69	2000	[18, 186, 187]
112.	kaempferol-3- <i>O</i> -[2- <i>O</i> -( <i>E</i> -6- <i>O</i> -feruloyl)- $\beta$ -D-glucopyranosyl]- $\beta$ -D-galactopyranoside	C <sub>37</sub> H <sub>38</sub> O <sub>19</sub>	786.69	2007	[34, 188]
113.	(+) dihydroquercetin	C <sub>15</sub> H <sub>12</sub> O <sub>6</sub>	288.26	2023	[24]
114.	(+) aromadendrin	C <sub>15</sub> H <sub>12</sub> O <sub>5</sub>	272.26	2023	[24]
<b>Athraquinones</b>					
115.	1,3-dihydroxy-2-methyl anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2008	[190]
116.	1,7-dihydroxy-6-methoxy-2-methyl anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>5</sub>	284.27	2008	[190]
117.	1-hydroxy-2-methoxy-3-methyl-9,10-anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	268.27	2022	[19]
118.	1-hydroxy-4-methoxy anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2013	[191]
119.	2-hydroxymethyl-1-hydroxy anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2013	[191]
120.	robustaquinone B	C <sub>17</sub> H <sub>14</sub> O <sub>5</sub>	298.29	2022	[19]
121.	physcion	C <sub>16</sub> H <sub>12</sub> O <sub>5</sub>	284.27	2022	[19]
122.	erythroglauicin	C <sub>16</sub> H <sub>12</sub> O <sub>6</sub>	300.27	2022	[19]
123.	2-hydroxy-1,3-dimethoxy anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>5</sub>	284.27	2005	[37]
124.	2-hydroxy-3-methyl-1-methoxy anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	268.27	2007	[192]

125.	2-hydroxy-3-methyl-4-methoxy anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	268.27	2014	[193]
126.	2-hydroxy-7-methyl-3-methoxy anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	268.27	2007	[192]
127.	2-hydroxy-1-methoxy-3-methyl anthraquinone	C <sub>17</sub> H <sub>14</sub> O <sub>5</sub>	298.29	2007	[184]
128.	2-hydroxy-3-methyl anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>3</sub>	238.24	2008 2014	[173, 181]
129.	2-hydroxy-1-methoxy anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2014 2005	[37, 181]
130.	2-hydroxy-4-methoxy anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2008	[194]
131.	2-hydroxy-6-methyl anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>3</sub>	238.24	2008	[195]
132.	2-hydroxy-3-methoxy-6-methyl anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	268.27	2008	[195]
133.	2-hydroxy-3-hydroxymethyl-9,10-anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2022	[19]
134.	2-hydroxy-6-hydroxymethyl anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2022	[19]
135.	2-hydroxy-7-hydroxymethyl -3-methoxy anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>5</sub>	284.27	2008	[196]
136.	2,6-dihydroxy-3-methyl-9,10-anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2022	[19]
137.	2,6-dihydroxy-3-methyl-4-methoxy anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>5</sub>	284.27	2006	[197]
138.	2,6-dihydroxy-1-methoxy-3-methyl anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>5</sub>	284.27	2007	[184]
139.	2,7-dihydroxy-3-methyl anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2008	[198]
140.	3-hydroxy-2-methyl anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>3</sub>	238.24	2006	[17]
141.	3-hydroxy-2-hydroxymethyl anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub>	254.24	2023	[24]
142.	rubiadin-1-methyl ether	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	268.27	2023	[24]
143.	3-hydroxy-2-methyl-4-methoxy anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	268.27	1979	[199]
144.	3-hydroxy-2-methoxy-6-methyl-9,10-anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	268.27	2022	[19]
145.	3-hydroxy-2-methoxy-6-hydroxymethyl-9,10-anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>5</sub>	284.27	2022	[19]
146.	tectoquinone	C <sub>15</sub> H <sub>10</sub> O <sub>2</sub>	224.26	2022	[19]
147.	2-methyl-3-methoxy anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>4</sub>	252.27	2006	[17]
148.	2-methoxy anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>3</sub>	238.24	2023	[24]
149.	2-methoxy-3-methyl-9,10-anthraquinone	C <sub>16</sub> H <sub>12</sub> O <sub>3</sub>	252.27	2022	[19]
150.	2,3-dimethoxy-6-methyl anthraquinone	C <sub>17</sub> H <sub>14</sub> O <sub>4</sub>	282.30	1986	[200]
151.	2-formyl-9,10-anthraquinone	C <sub>16</sub> H <sub>10</sub> O <sub>3</sub>	250.25	2022	[19]
152.	2-hydroxymethyl anthraquinone	C <sub>15</sub> H <sub>10</sub> O <sub>3</sub>	238.24	2013	[191]
153.	capitellataquinone D	C <sub>21</sub> H <sub>18</sub> O <sub>4</sub>	334.37	2022	[19]
154.	diffusaquinone A	C <sub>20</sub> H <sub>16</sub> O <sub>3</sub>	304.35	2022	[19]
155.	diffusaquinone B	C <sub>21</sub> H <sub>20</sub> O <sub>4</sub>	336.39	2022	[19]

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156.	diffusaquinone C	C <sub>21</sub> H <sub>20</sub> O <sub>5</sub>	352.39	2022	[19]
157.	diffusaquinone D	C <sub>20</sub> H <sub>16</sub> O <sub>3</sub>	304.35	2022	[19]
158.	diffusaquinone E	C <sub>20</sub> H <sub>16</sub> O <sub>4</sub>	320.34	2022	[19]
159.	diffusaquinone F	C <sub>20</sub> H <sub>16</sub> O <sub>5</sub>	336.34	2022	[19]
160.	diffusaquinone G	C <sub>20</sub> H <sub>16</sub> O <sub>5</sub>	336.34	2022	[19]
<b>Phenolic acids</b>					
161.	3,4-dihydroxy benzoic acid	C <sub>7</sub> H <sub>6</sub> O <sub>4</sub>	154.12	2007	[34]
162.	4-hydroxy-3-methoxy benzoic acid	C <sub>8</sub> H <sub>8</sub> O <sub>4</sub>	168.15	2012	[20]
163.	4-hydroxy benzoic acid	C <sub>7</sub> H <sub>6</sub> O <sub>3</sub>	138.12	2012	[20]
164.	4-hydroxy-3,5-dimethoxy benzoic acid	C <sub>9</sub> H <sub>10</sub> O <sub>5</sub>	198.17	2012	[20]
165.	<i>p</i> -coumaric acid	C <sub>9</sub> H <sub>8</sub> O <sub>3</sub>	164.16	2005	[17, 37]
166.	<i>p</i> -coumaric acid- <i>O</i> -glucopyranside	C <sub>15</sub> H <sub>18</sub> O <sub>8</sub>	326.30	2014	[182]
167.	caffeic acid	C <sub>9</sub> H <sub>8</sub> O <sub>4</sub>	180.16	2007	[34]
168.	caffeoyl hexoside	C <sub>15</sub> H <sub>18</sub> O <sub>9</sub>	342.30	2014	[182]
169.	ferulic acid	C <sub>10</sub> H <sub>10</sub> O <sub>4</sub>	194.19	2008	[190]
170.	ferulic acid hexoside	C <sub>16</sub> H <sub>20</sub> O <sub>9</sub>	356.33	2014	[182]
171.	<i>p</i> -methoxy cinnamic acid	C <sub>10</sub> H <sub>10</sub> O <sub>3</sub>	178.19	1996	[40]
172.	methoxy-cinnamoyl hexoside	C <sub>16</sub> H <sub>20</sub> O <sub>8</sub>	340.33	2017	[201]
173.	octadecyl ( <i>E</i> )- <i>p</i> -coumarate	C <sub>27</sub> H <sub>44</sub> O <sub>3</sub>	416.33	2008	[202]
174.	3-caffeoyl quinic acid	C <sub>16</sub> H <sub>18</sub> O <sub>9</sub>	354.31	2014	[182]
175.	4-caffeoyl quinic acid	C <sub>16</sub> H <sub>18</sub> O <sub>9</sub>	354.31	2014	[182]
176.	5-caffeoyl quinic acid	C <sub>16</sub> H <sub>18</sub> O <sub>9</sub>	354.31	2014	[182]
177.	3- <i>p</i> -coumaroyl quinic acid	C <sub>16</sub> H <sub>18</sub> O <sub>8</sub>	338.31	2014	[182]
178.	4- <i>p</i> -coumaroyl quinic acid	C <sub>16</sub> H <sub>18</sub> O <sub>8</sub>	338.31	2014	[182]
179.	5- <i>p</i> -coumaroyl quinic acid	C <sub>16</sub> H <sub>18</sub> O <sub>8</sub>	338.31	2014	[182]
180.	3-feruloyl quinic acid	C <sub>17</sub> H <sub>20</sub> O <sub>9</sub>	368.34	2014	[182]
181.	4-feruloyl quinic acid	C <sub>17</sub> H <sub>20</sub> O <sub>9</sub>	368.34	2014	[182]
182.	5-feruloyl quinic acid	C <sub>17</sub> H <sub>20</sub> O <sub>9</sub>	368.34	2014	[182]
183.	4,4'-dihydroxy- $\alpha$ -truxillic acid	C <sub>18</sub> H <sub>16</sub> O <sub>6</sub>	328.32	1996	[40]
184.	4,4'-dimethoxyl- $\alpha$ -truxillic acid	C <sub>20</sub> H <sub>20</sub> O <sub>6</sub>	356.37	1980	[41]
<b>Volatile oils</b>					
185.	6,10,14-trimethyl-2-pentadecanone	C <sub>18</sub> H <sub>36</sub> O	268.49	2005	[21]
186.	phytol	C <sub>20</sub> H <sub>40</sub> O	296.54	2005	[21]
187.	$\alpha$ -cedrol	C <sub>15</sub> H <sub>26</sub> O	222.37	2005	[21]
188.	tetradecanoic acid	C <sub>20</sub> H <sub>31</sub> NO <sub>4</sub>	349.47	2005	[21]
189.	hexadecanoic acid methyl ester	C <sub>17</sub> H <sub>34</sub> O <sub>2</sub>	270.46	2005	[21]
190.	hexadecanoic acid	C <sub>16</sub> H <sub>32</sub> O <sub>2</sub>	256.46	2005	[21]
191.	1,2-benzenedicarboxylic acid isobutyl ester	C <sub>11</sub> H <sub>12</sub> O <sub>4</sub>	208.21	2005	[21]
192.	1,2-benzenedicarboxylic acid bis(2-methylpropyl)ester	C <sub>14</sub> H <sub>18</sub> O <sub>4</sub>	250.29	2005	[21]
193.	9,12,15-octadecatrienoic acid methyl ester	C <sub>19</sub> H <sub>32</sub> O <sub>2</sub>	292.46	2005	[21]
194.	9-octadecenoic acid	C <sub>18</sub> H <sub>34</sub> O <sub>2</sub>	282.47	2005	[21]
195.	9,12-octadecenoic acid	C <sub>19</sub> H <sub>34</sub> O <sub>2</sub>	294.48	2005	[21]

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

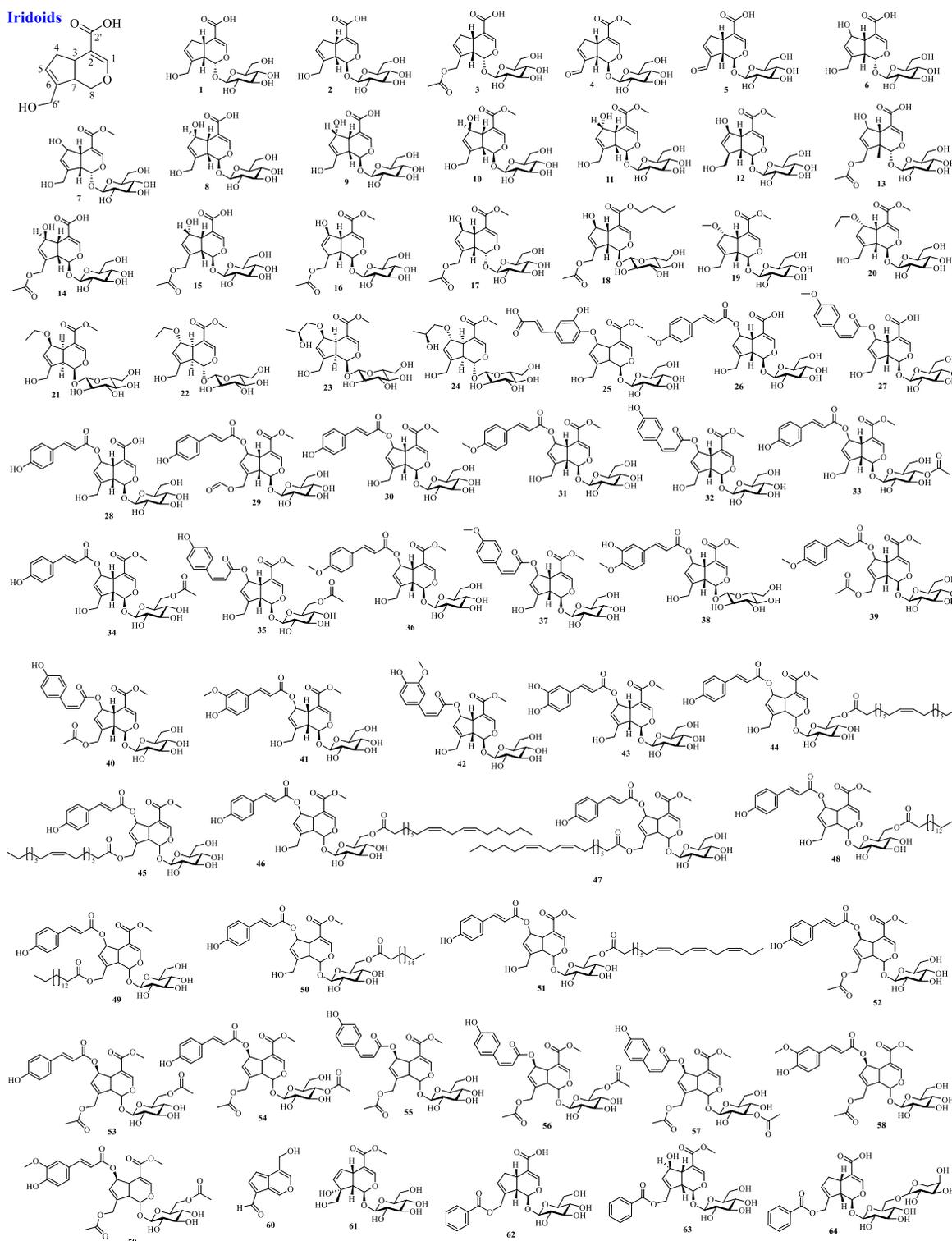
239.	HDP2	-	-	2019	[44, 45]
240.	HDP3	-	-	2022	[46]
<b>Cyclic peptides</b>					
241.	CD1	-	-	2015	[23]
242.	CD2	-	-	2015	[23]
243.	CD3	-	-	2015	[23]
<b>Other compounds</b>					
244.	10( <i>S</i> )-hydroxy pheophytin	C <sub>55</sub> H <sub>82</sub> N <sub>4</sub> O <sub>6</sub>	895.28	2010	[206]
245.	aurantiamide acetate	C <sub>27</sub> H <sub>28</sub> N <sub>2</sub> O <sub>4</sub>	444.53	2008	[202]
246.	shecaocerenoside A	C <sub>48</sub> H <sub>93</sub> NO <sub>9</sub>	828.27	2017	[32]
247.	hedyocerenoside F	C <sub>46</sub> H <sub>89</sub> NO <sub>9</sub>	800.22	2018	[60]
248.	hedyocerenoside G	C <sub>40</sub> H <sub>77</sub> NO <sub>9</sub>	716.05	2018	[60]
249.	hedyoceramide A	C <sub>31</sub> H <sub>61</sub> NO <sub>5</sub>	527.83	2018	[60]
250.	hedyoceramide B	C <sub>37</sub> H <sub>71</sub> NO <sub>4</sub>	593.98	2018	[60]
251.	9- <i>O</i> -( <i>trans-p</i> -coumaroyl)-alternariol	C <sub>24</sub> H <sub>18</sub> O <sub>6</sub>	402.40	2023	[24]
252.	9- <i>O</i> -( <i>trans</i> -caffeoyl)-alternariol	C <sub>24</sub> H <sub>18</sub> O <sub>7</sub>	418.40	2023	[24]
253.	daucosterol	C <sub>29</sub> H <sub>50</sub> O	414.72	2006	[17]
254.	$\beta$ -sitosterol	C <sub>34</sub> H <sub>58</sub> O <sub>6</sub>	562.83	2006	[17]
255.	stigmasterol	C <sub>29</sub> H <sub>48</sub> O <sub>2</sub>	428.70	2006	[17, 173]
256.	stigmasterol-5,2-diene-3 $\beta$ , 7 $\alpha$ -glycol	C <sub>29</sub> H <sub>46</sub> O	410.69	2002	[207]
257.	7-hydroxy-6-methoxy-coumarin	C <sub>9</sub> H <sub>6</sub> O <sub>4</sub>	178.14	2008	[173]
258.	esculetin	C <sub>10</sub> H <sub>8</sub> O <sub>4</sub>	192.17	2008	[202]
259.	4,7-dimethoxy-5-methyl-1,3-benzodioxole	C <sub>10</sub> H <sub>12</sub> O <sub>4</sub>	196.20	2022	[19]

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

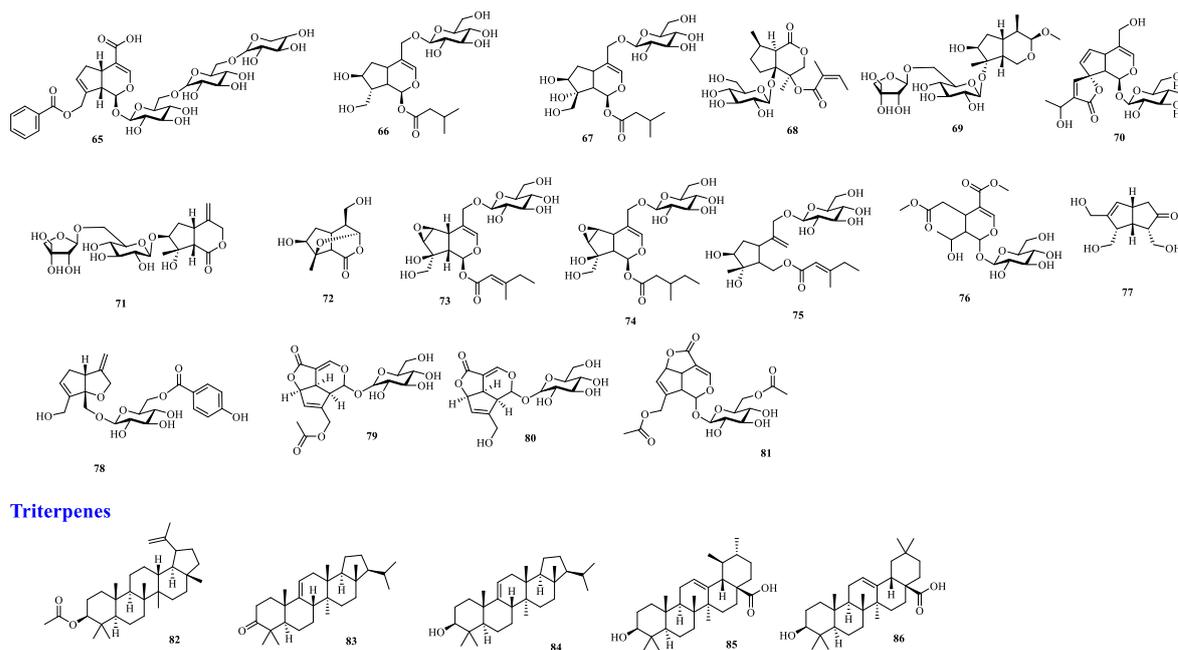
#### 4.1. Iridoids and Triterpenoids

Terpenoids are compounds derived from mevalonic acid (MVA) with the general formula (C<sub>5</sub>H<sub>8</sub>)<sub>n</sub>. 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  $\beta$ -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].

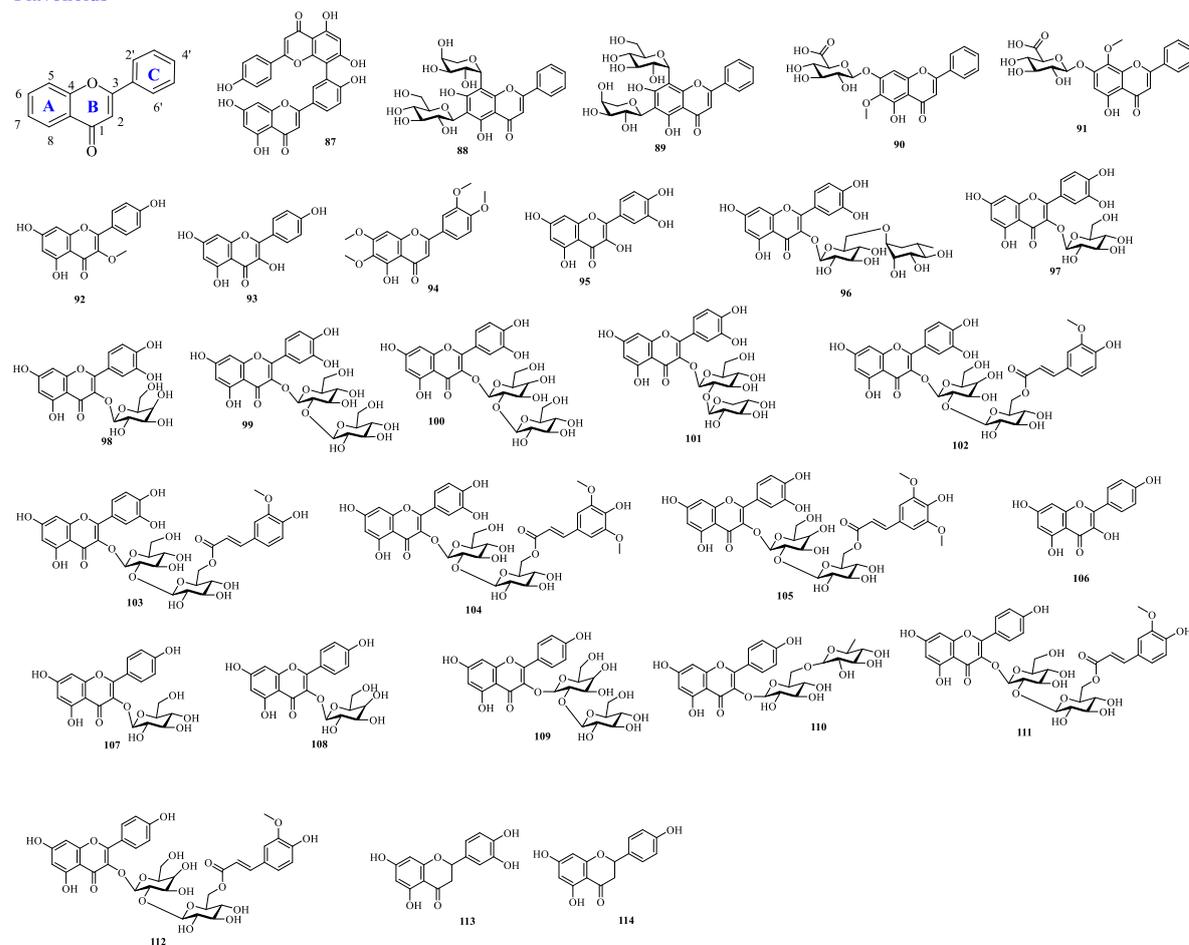


**Figure 5.** Structure of iridoids and triterpenes in SD (*continued.*)

*Scleromitron diffusum*: A comprehensive review**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].

## Flavonoids



**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 anthracene, 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].

## Athraquinones

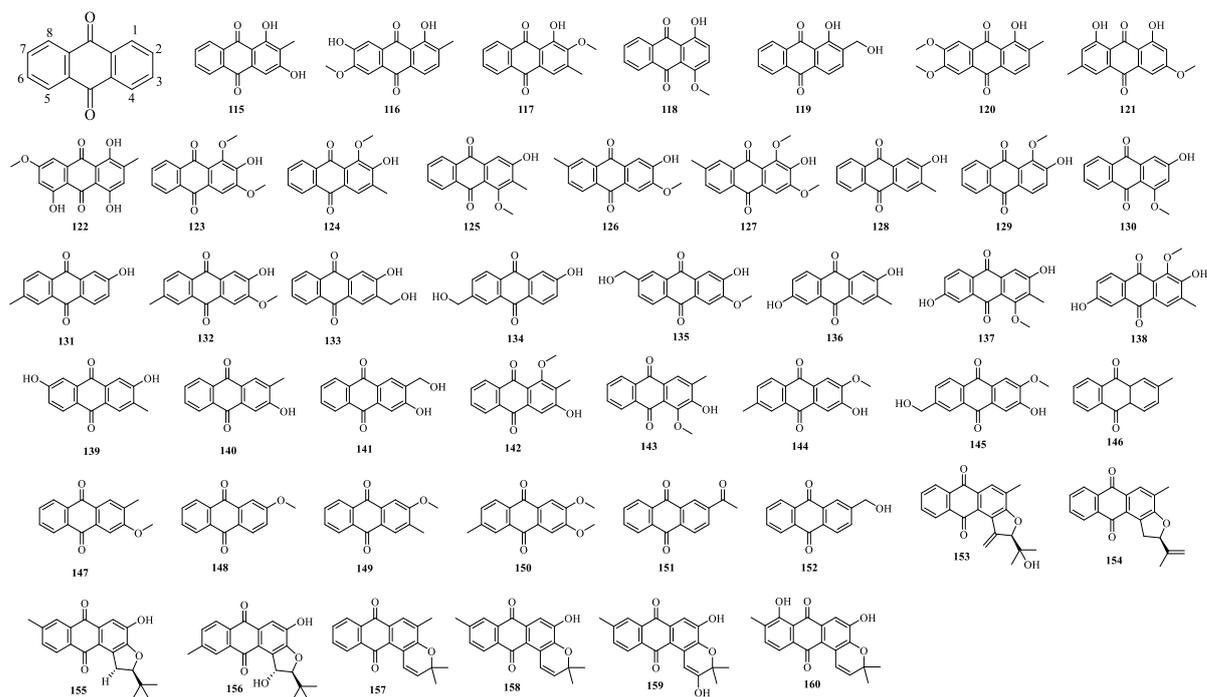


Figure 7. Structure of athraquinones in SD

## 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.

## Phenolic acids

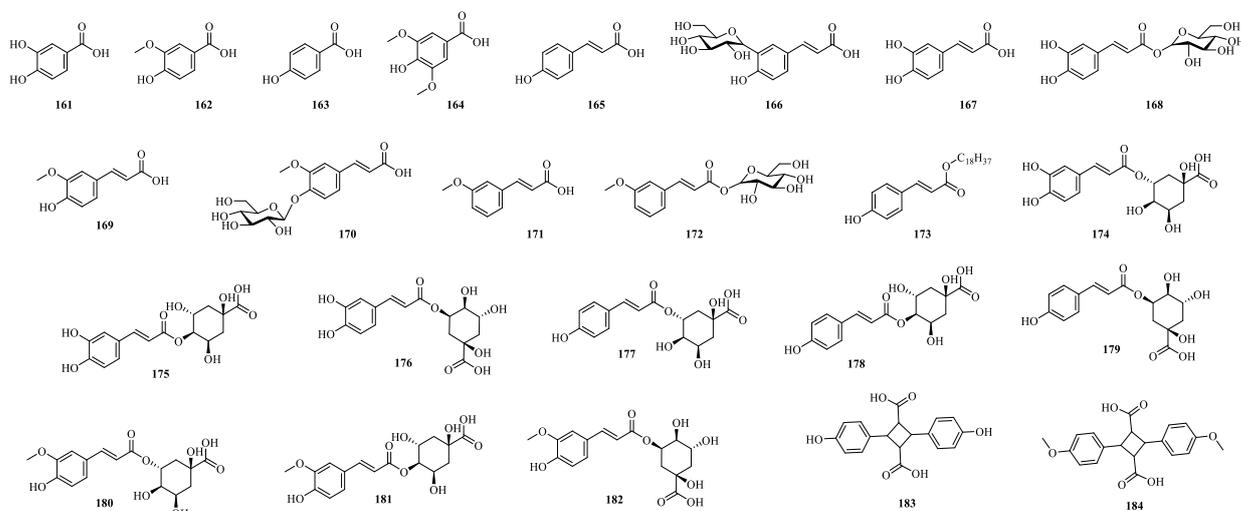
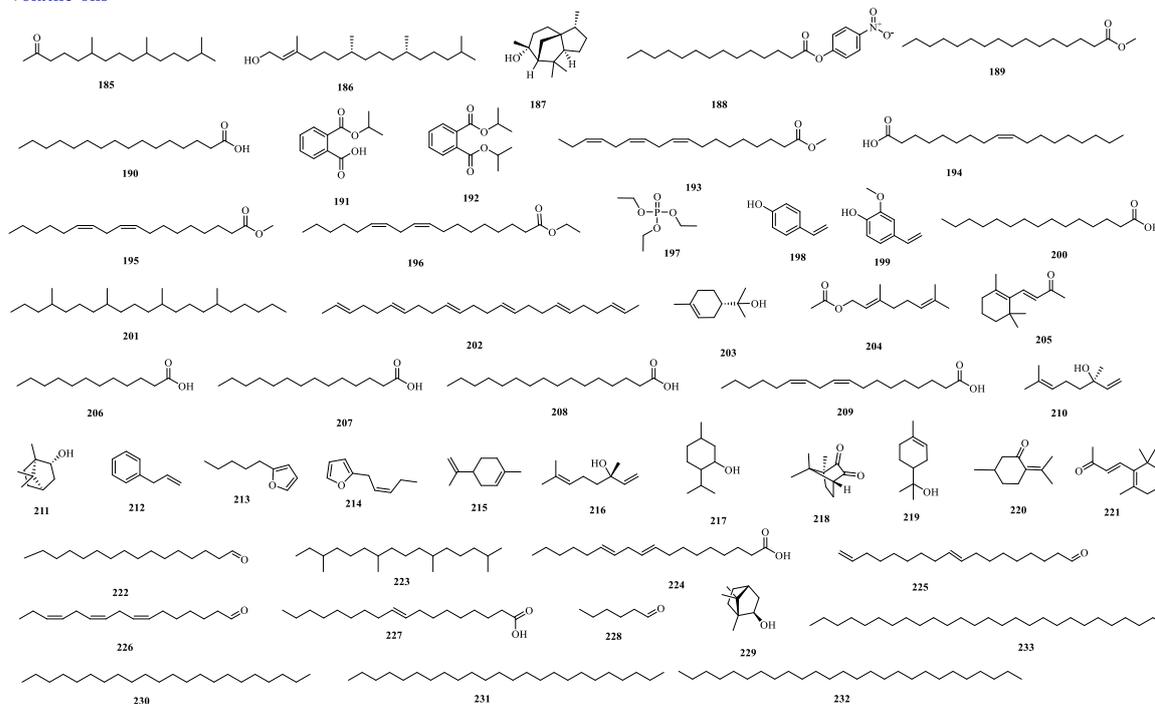


Figure 8. Structure of phenolic acids in SD

#### 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.

##### Volatile oils

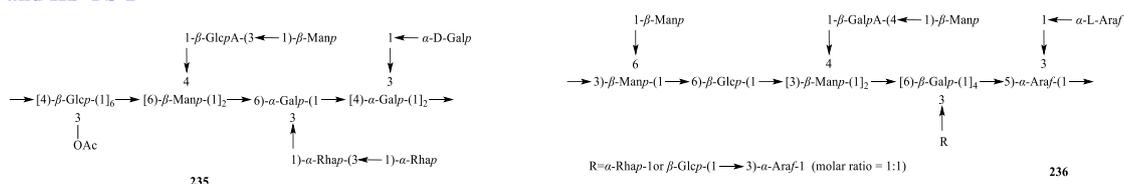


**Figure 9.** Structure of volatile oil components in SD

#### 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

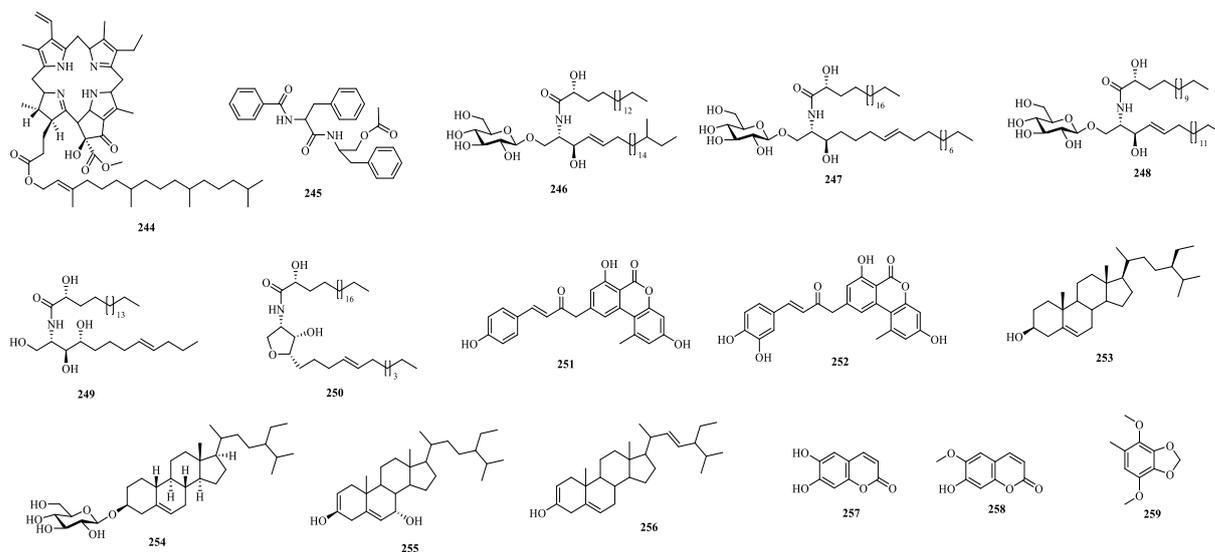
## 4.7. Cyclic Peptides

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 GAFLKCGESCIVYLPCLTTVVGCSQCNSVCYRD, 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<sub>50</sub> 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-methylantraquinone (**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].

Hedyoidridoside 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<sub>50</sub> 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- $\beta$ , 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- $\beta$  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- $\beta$ -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- $\kappa$ B. 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,  $\beta$ -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<sub>50</sub> values of approximately 50  $\mu$ M and 65  $\mu$ M, respectively. This compound was shown to enhance the sub-G1 apoptotic. The mechanism involves the activation of caspases and the phosphorylation of GSK 3 $\beta$  [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 ( $\mu$ PA), 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  $\beta$ -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, cyto, 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  $\mu$ g/mL), researchers found that SD significantly increased the proportion of CD3<sup>+</sup>CD56<sup>+</sup> CIK cells, indicating enhanced activation of these immune cells. However, there was no notable change in the proportions of CD4<sup>+</sup>, CD8<sup>+</sup>, or CD4<sup>+</sup>CD25<sup>+</sup> CIK cells. Furthermore, SD-treated CIK cells demonstrated a heightened capacity to kill tumor cells and exhibited increased production of interferon- $\gamma$  and tumor necrosis factor- $\alpha$  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<sub>50</sub> 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<sub>2</sub>O<sub>2</sub>-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  $\beta$ -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 $\beta$ -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  $\beta$ -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-

$1\beta$ -induced pro-inflammatory factors, including COX2, iNOS, IL-6, TNF- $\alpha$ , 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- $\alpha$  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- $\kappa$ B 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- $\gamma$ . 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 HNF1 $\alpha$ , 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- $\alpha$ , IL-1 $\beta$ , IL-6, and monocyte chemoattractant 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- $\alpha$ , IL-6, and IL-1 $\beta$  in a concentration-dependent manner without causing cytotoxicity. Furthermore, SD suppressed the mRNA expression of iNOS, TNF- $\alpha$ , IL-6, and IL-1 $\beta$  in LPS-stimulated RAW 264.7 cells. The authors hypothesized that SD may exert its anti-inflammatory activity by inhibiting the NF- $\kappa$ B 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- $\alpha$  stimulated serum nitrite accumulation in RAW 264.7 cells. Further investigations revealed that the aqueous extract inhibited the expression of iNOS and IL-1 $\alpha$  in a concentration-dependent manner, while promoting the expression of HO-1 and PPAR- $\alpha$ . 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- $\kappa$ B and caspase-1. Additionally, SD improved the expression of inflammatory mediators, including TNF- $\alpha$ , 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 $\beta$ , TNF- $\alpha$ , and TGF- $\beta$  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<sub>50</sub> values of 5.69, 6.16, and 6.84  $\mu$ M, 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-isopropylidihydrofuran 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 $\beta$  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 $\beta$  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)- $\beta$ -D-glucopyranosyl]- $\beta$ -D-glucopyranoside (**103**) exhibited the strongest inhibitory effect on cholinesterase,  $\beta$ -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	<i>In Vitro/In Vivo</i>	Pathway or possible target site	Ref.
Anticancer	SKM-1 cells	0, 25, 50, 75, 100 and 125 µg/mL	<i>In Vitro</i>	PI3K/Akt pathway, caspase-3-8,-9↑	[25]
	U937 cells	0, 20, 40 and 80 µM	<i>In Vitro</i>	p-ERK1/2↓, p-P38mapk, caspase-3↑	[48]
	THP-1 cells	50 µM	<i>In Vitro</i>	Fas/FasL, DR4, TRAIL, caspase-8↑	[50]
	Hep-G2 cells	20 mg/mL	<i>In Vitro</i>	AKT/mTOR pathway;	[51]
	A459, HepG2, PC-3, CNE-2 and BCG-823 cells	1.0 µM to 300 µM	<i>In Vitro</i>	-	[32]
	HepG2, Hep3B, HCCLM3 cells	12.5, 20, 25 µg/mL	<i>In Vitro</i>	PERK-eIF2 $\alpha$ -ATF4 signaling pathway	[53]
	Rats	200 mg/mL	<i>In Vivo</i>	ALT、AST、ALP↓	[55]
	HepG2 cells	0, 1.25, 2.5, 5 and 10 mg/mL	<i>In Vitro</i>	CDK2, cyclin E and E2F1↓	[56]
	A549 cells	0, 20, 40 and 80 µM	<i>In Vitro</i>	JAK2/STAT3 pathway; MMP-1, MMP-2, MMP-9, IL-6, G-CSF, IL-6R, IL-8, MCP-1, RANTES, TNF- $\alpha$ ↓	[61]
	mouse peritoneal macrophages	1 mg/mL	<i>In Vitro</i>	TNF- $\alpha$ ,NO↑	[57]
	A549 cells	25, 50 and 100 µg/mL	<i>In Vitro</i>	EMT, N-cadherin and vimentin↓ E-cadherin, TIMP-2, TIMP-9↑	[44]
	A549 cells	25、100 and 200 µg/mL	<i>In Vitro</i>	caspase-9, -3↑, Bax/Bcl-2 ↓	[45]
	A549 and H1299 cells	0, 10, 20, 40 and 80 µmol/mL	<i>In Vitro</i>	PI3K/AKT/mTOR signaling pathway	[59]
	CD8 and Treg cells	20 mg/kg	<i>In Vitro</i>	PI3K-AKT, MAPK pathway	[63]
	HT-29 cells	0, 1, 3 and 5 mg/mL	<i>In Vitro</i>	caspase-9, caspase-3, Bax, Bcl-2↑	[67]
	HT-29 cells	1, 3 and 5 mg/mL	<i>In Vitro</i>	IL-6/STAT3 signaling pathway; STAT3↑, Cyclin D1, Bcl-2↓	[68]

HCT-8/5-FU cell	0, 0.5, 1 and 2 mg/mL	<i>In Vitro</i>	E-cadherin $\uparrow$ , TGF- $\beta$ , SMAD4 and N-cadherin $\downarrow$	[66]
nude mouse and HT-29 cells	3 g/kg	<i>In Vitro</i> and <i>in Vivo</i>	STAT3 pathway	[69]
CRC mice	6 g/kg	<i>In Vivo</i>	STAT3 pathway; p21, Bax $\uparrow$ , Cyclin D1, CDK4, Bcl-2 $\downarrow$	[70]
HT-29, SW620 and HCT116 cells	1 mg/mL	<i>In Vitro</i>	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	<i>In Vitro</i>	P-gp, ABCG2 $\downarrow$	[72]
HCT-8 cells	0, 0.25, 0.5, 1 mg/mL	<i>In Vitro</i>	N-cadherin, vimentin $\uparrow$ TGF- $\beta$ , p-Smad2/3, Smad4, E-cadherin $\downarrow$	[73]
HCT116 cells	0, 20, 40 $\mu$ M	<i>In Vitro</i>	miR-4500 $\uparrow$ , STAT3 $\downarrow$	[74]
HT-29 cells	0, 0.5, 1 and 2 mg/mL	<i>In Vitro</i>	Bax $\uparrow$ , COX-2, Inos, eNOS, HIF-1 $\alpha$ , Bcl-2 $\downarrow$	[77]
MCF-7 cells	0, 10, 30, 50, 70 and 100 $\mu$ g/mL	<i>In Vitro</i>	ERK1/2 MAPK pathways; Bax $\uparrow$ , Bcl-2, MMP-9, ICAM-1, p-p38 $\downarrow$	[78]
4T1 cells	25 g/kg	<i>In Vitro</i>	cAMP, miR-200c $\uparrow$ PDE7B, PD-L1, $\beta$ -catenin, cyclin D1 $\downarrow$	[79]
MCF-7 cells	30 $\mu$ M	<i>In Vitro</i>	Ca <sup>2+</sup> /calpain/caspase-4 pathway	[81]
U87 cells	0, 4, 8 mg/mL	<i>In Vitro</i>	caspase-3, Bcl-2, Bax, ERK $\downarrow$	[83]
SGC-7901 cells	25, 50 and 100 $\mu$ g/mL	<i>In Vitro</i> and <i>in Vivo</i>	RUNX3 $\uparrow$	[84]
GBC cell	25, 50, and 100 $\mu$ g/mL	<i>In Vitro</i>	PI3K/Akt, Wnt, HIF-1, focal adhesion, microRNAs pathway	[86]

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

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

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

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### Competing Interests

The authors declare that there is no conflict of interest.

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### References

- [1] P.B. Drašar (2022). Plant secondary metabolites used for the treatment of diseases and drug development, *Biomedicines* **10**, 576.
- [2] O. Kayser (2018). Ethnobotany and medicinal plant biotechnology: from tradition to modern aspects of drug development, *Planta Med.* **8**, 834-838.
- [3] C. Colalto (2018). What phytotherapy needs: Evidence-based guidelines for better clinical practice, *Phytother. Res.* **32**, 413-425.
- [4] H. Sardarabadi, M. H. Darvishi, F. Zohrab and H. Javadi (2024). Nanophytomedicine: A promising practical approach in phytotherapy, *Phytother. Res.* **38**, 3607-3644.

- [5] Z. L. Zhang, Y. Z. Li, G. Q. Wu, D. D. Zhang, C. Deng, Z. M. Wang, X. M. Song and W. Wang (2022). A comprehensive review of traditional uses, phytochemistry and pharmacology of Reynoutria genus, *J. Pharm. Pharmacol.* **74**, 1718-1742.
- [6] Z. L. Zhang, Y. Z. Li, G. Q. Wu, Y. M. Li, D. D. Zhang and R. Wang (2023). A comprehensive review of phytochemistry, pharmacology and clinical applications of uncariae ramulus cum uncis, *Arab. J. Chem.* **16**, 104638.
- [7] P. M. Leite, L. M. Camargos and R. O. Castilho (2021). Recent progress in phytotherapy: A Brazilian perspective, *Eur. J. Integr. Med.* **41**, 101270.
- [8] I. E. Cock, A. Orchard, C. Nhlabathi, T. Nxumalo and S. Van Vuuren (2022). The feasibility of southern African traditional plant therapies for ophthalmic use, *S. Afr. J. Bot.* **148**, 360-378.
- [9] V. S. S. Kantamreddi, S. Parida, S. M. Kommula and C. W. Wright (2009). Phytotherapy used in orissa state, india for treating malaria, *Phytother. Res.* **23**, 1638-1641.
- [10] L. You, K. Liang, R. An and X. Wang (2022). The path towards FDA approval: A challenging journey for Traditional Chinese Medicine, *Pharmacol. Res.* **182**, 106314.
- [11] E. L. H. Leung and S. Xu (2020). Traditional Chinese medicine in cardiovascular drug discovery, *Pharmacol. Res.* **160**, 105168.
- [12] H. H. Gao, L. F. Qin, X. Zhang, X. Yuan, Z. M. Feng, J. S. Jiang, P. C. Zhang and Y. N. Yang (2024). Six new iridoid glycosides from the whole plants of *Hedyotis diffusa*, *J. Asian Nat. Prod. Res.* **26**, 112-119.
- [13] S. Maluf, J. V. Salgado, D. N. Cysne, D. M. F. Camelo, J. R. Nascimento, B. V. T. Maluf, L. D. M. Silva, M. R. d.C. Belfort, L. A. Silva, R. N. M. Guerra, N. Salgado Filho and F. R. F. Nascimento (2020). Increased glycated hemoglobin levels in patients with *Helicobacter pylori* infection are associated with the grading of chronic gastritis, *Front. Immunol.* **11**, 2121.
- [14] E.S. Levitskaya, M. M. Batiushin, A. V. Khripoun, Y. A. V. Kulikovskikh, M. A. Akimenko and O. V. Voronova (2020). Analysis of the influence of clinical and morphological parameters on the risk of small-diameter renal artery fibroelastosis in arterial hypertension and primary chronic glomerulonephritis, *Eur. Heart J.* **41**, 2719.
- [15] W. S. Wang (2014). Clinical observation on the treatment of psoriasis vulgaris in the progressive stage (blood-heat syndrome) by adding flavor dermatitis soup, *Heilongjiang Univ. Trad. Chinese Medicin.* 2014.
- [16] R. Chen, J. He, X. Tong, L. Tang and M. Liu (2016). The *Hedyotis diffusa* Willd. (Rubiaceae): a review on phytochemistry, pharmacology, quality control and pharmacokinetics, *Molecules* **21**, 710.
- [17] J. Y. Si, D. H. Chen, R. L. Pan and X. H. Zhao (2006). Chemical constituents of *Hedyotis diffusa*, *Nat. Prod. Res Dev.* **18**, 942-944.
- [18] D. X. Li and O. J. Schmitz (2015). Comprehensive two-dimensional liquid chromatography tandem diode array detector (DAD) and accurate mass QTOF-MS for the analysis of flavonoids and iridoid glycosides in *Hedyotis diffusa*, *Anal. Bioanal. Chem.* **407**, 231-240.
- [19] H. Y. Hung, K. C. Cheng, P. C. Kuo, I. T. Chen, Y. C. Li, T. L. Hwang, S. H. Lam and T. S. Wu (2022). Chemical constituents of *Hedyotis diffusa* and their anti-inflammatory bioactivities, *Antioxidants* **11**, 335.
- [20] S. Y. Liu, F. L. Chen, Q. F. Tang, J. B. Luo and Y. C. Zeng (2012). Study of chemical constituents from herba *Hedyotis diffusae*, *Tradi. Chin. Drug Res. Clin. Pharmacol.* **1**, 1-6.
- [21] Z. G. Liu, J. B. Luo and F. L. Chen (2005). The pilot study of volatile compounds in *Hedyotis diffusa* from different sources, *Tradit. Chin. Drug Res. Clin. Pharm.* **1**, 132-134.

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- [22] J. Huo, Y. Lu, Y. Jiao and D. Chen (2020). Structural characterization and anticomplement activity of an acidic polysaccharide from *Hedyotis diffusa*, *Int. J. Bio. Macromol.* **155**, 1553-1560.
- [23] E. Hu, D. Wang, J. Chen and X. Tao (2015). Novel cyclotides from *Hedyotis diffusa* induce apoptosis and inhibit proliferation and migration of prostate cancer cells, *Int. J. Clin. Exp. Med.* **8**, 4059-4065.
- [24] Y. Lv and Y. Wang (2023). Chemical constituents from *Oldenlandia diffusa* and their cytotoxic effects on human cancer cell lines, *Nat. Prod. Res.* **37**, 397-403.
- [25] J. Jiang, B. Wang, J. Li, B. Ye, S. Lin, W. Qian and L. Shan and T. Efferth (2017). Total coumarins of *Hedyotis diffusa* induces apoptosis of myelodysplastic syndrome SKM-1 cells by activation of caspases and inhibition of PI3K/Akt pathway proteins, *J. Ethnopharmacol.* **196**, 253-260.
- [26] J. Li, D. Liu, D. Li, Y. Guo, H. Du and Y. Cao (2022). Phytochemical composition and anti-aging activity of butanol extract of *Hedyotis diffusa* in *Caenorhabditis elegans*, *Chem. Biodivers.* **1**, 19e202100685.
- [27] L. Zhao, J. Deng, Z. J. Xu, W. P. Zhang, M. M. Khalil, N. A. Karrow and L. H. Sun (2021). Mitigation of aflatoxin B1 hepatotoxicity by dietary *Hedyotis diffusa* is associated with activation of NRF2/ARE signaling in chicks, *Antioxidants* **10**, 878.
- [28] H. Deng, J. Jiang, S. Zhang, L. Wu, Q. Zhang and W. Sun (2023). Network pharmacology and experimental validation to identify the potential mechanism of *Hedyotis diffusa* Willd against rheumatoid arthritis, *Sci. Rep.* **13**, 1425.
- [29] D. Q. Li, Y. J. Guo, Z. C. P., H. Du, Y. Hong, B. Huang and Y. Cao (2021). N-butanol extract of *Hedyotis diffusa* protects transgenic *Caenorhabditis elegans* from A $\beta$ -induced toxicity, *Phytother. Res.* **35**, 1048-1061.
- [30] Z. Q. Mao, N. Minakawa and M. L. Moi (2022). Novel Antiviral efficacy of *Hedyotis diffusa* and *Artemisia capillaris* extracts against dengue virus, Japanese encephalitis virus, and Zika virus infection and immunoregulatory cytokine signatures, *Plants* **11**, 2589.
- [31] D. Zhang, Z. Zhang, G. Wu, Y. Sun, Y. Jiang, H. Zhang, W. Wang, X. Song and Y. Li (2022). Iridoids and lignans from *Valeriana officinalis* L. and their cytotoxic activities, *Phytochem. Lett.* **49**, 125-130.
- [32] C. Wang, X. Zhou, Y. Wang, D. Wei, C. Deng, X. Xu, P. Xin and S. Sun (2017). The antitumor constituents from *Hedyotis diffusa* Willd., *Molecules* **32**, 2120.
- [33] B. Ding, W. W. Ma, Y. Dai, H. Gao, Y. Yu, Y. Tao, Y. Zhong and X. S. Yao (2010). Biologically active iridoids from *Hedyotis diffusa*, *Helv. Chim. Acta* **93**, 2488-2494.
- [34] J. Z. Liu and L. Wang (2007). Study the chemical constituents of *Hedyotis diffusa* Willd., *J. Hebei Med. Univ.* **3**, 188-190.
- [35] B. Yang, H. Liu, J. Yang, V. K. Gupta and Y. Jiang (2018). New insights on bioactivities and biosynthesis of flavonoid glycosides, *Trends. Food Sci. Technol.* **79**, 116-124.
- [36] G. H. Xu, Y. H. Kim, S. W. Chi, S. J. Choo, I. J. Ryoo, J. S. Ahn and I. D. Yoo (2010). Evaluation of human neutrophil elastase inhibitory effect of iridoid glycosides from *Hedyotis diffusa*, *Bioorg. Med. Chem. Lett.* **20**, 513-515.
- [37] K. S. Wu, K. Zhang, G. S. Tan, G. Y. Zeng and Y. J. Zhou (2005). Studies on constituents of *Oldenlandia diffusa*, *Chin. Pharm. J.* **40**, 817-819.
- [38] Z. Zhang, Y. Li, Q. Cheng, G. Wu, D. Zhang, W. Huang, C. Deng, Z. Wang and X. Song (2021). Chemical constituents from the roots of *Fallopia multiflora* var. *Ciliinerve*, *Biochem. Syst.Ecol.* **99**, 104340.

- [39] D. Zhang, Z. Zhang, G. Wu, Y. Sun, Y. Jiang, H. Zhang, X. Song, W. Wang and Y. Li (2022). Phenolic derivatives with cytotoxic activities from the roots of *Fallopia multiflora* var. *ciliinervis*, *Phytochem. Lett.* **52**, 72-75.
- [40] H.C. Lv and J. He (1996). A Study on chemical constituents of *Oldenlandia diffusa*, *Nat. Prod. Res. Dev.* **8**, 34-37.
- [41] P. H. Ruehle, C. E. Browne, E. H. Vickery, N. R. Beller, E. J. Eisenbraun, R. A. Loghry and D. Van der Helm (1980). Synthesis and antifertility activity of 3,9-dihydroxy-5,6,6alpha-6beta,11,12,12-beta, 12-alpha-octahydrodibenzo[a,g]biphenylene, a structural relative of diethylstilbestrol, *J. Med. Chem.* **23**, 1410-1414.
- [42] N. J. Sadgrove, G. F. Padilla-González, O. Leuner, I. Melnikovova and E. Fernandez-Cusimamani (2021). Pharmacology of natural volatiles and essential oils in food, therapy, and disease prophylaxis, *Front. Pharmacol.* **12**, 740302.
- [43] M. A. He, C. Y. Lin, Z. J. Jie, C. G. Shang and Y. P. Min (2014). Effect of preliminary immune activity and structural identification of a polysaccharide extracted from *Oldenlandia diffusa*, *Chin. J. Exp. Tradit. Med. Formula* **22**, 45-48.
- [44] L. Lin, K. Cheng, Z. He, Q. Lin, Y. Huang, C. Chen, Z. Xie, L. Chen and Z. Liang (2019). A polysaccharide from *Hedyotis diffusa* interrupts metastatic potential of lung adenocarcinoma A549 cells by inhibiting EMT via EGFR/Akt/ERK signaling pathways, *Int. J. Biol. Macromol.* **129**, 706-714.
- [45] L. Lin, K. Cheng, Z. Xie, C. Chen, L. Chen, Y. Huang and Z. Liang (2019). Purification and characterization a polysaccharide from *Hedyotis diffusa* and its apoptosis inducing activity toward human lung cancer cell line A549, *Int. J. Biol. Macromol.* **122**, 64-71.
- [46] C. Ma, Y. Wei, Q. Liu, Y. Xin, G. Cao, X. Wang and P. Yang (2019). Polysaccharides from *Hedyotis diffusa* enhance the antitumor activities of cytokine-induced killer cells, *Biomed. Pharmacother.* **117**, 109167.
- [47] N. L. Daly and D. T. Wilson (2021). Plant derived cyclic peptides, *Biochem. Soc. Trans.* **49**, 1279-1285.
- [48] N. Wang, D. Y. Li, H. Y. Niu, Y. Zhang, P. He and J. H. Wang (2013). 2-hydroxy-3-methylantraquinone from *Hedyotis diffusa* Willd induces apoptosis in human leukemic U937 cells through modulation of MAPK pathways, *Arch. Pharmacol Res.* **36**, 752-758.
- [49] H. S. Chung, H. J. Jeong, S. H. Hong, M. S. Kim, S. J. Kim, B. K. Song, I. S. Jeong, E. J. Lee, J. W. Ahn, S. H. Baek and H. M. Kim (2002). Induction of nitric oxide synthase by *Oldenlandia diffusa* in mouse peritoneal macrophages, *Biol. Pharm. Bull.* **25**, 1142-1146.
- [50] J. H. Wang, L. H. Shu, L. L. Yang, M. Zhang and P. He (2011). 2-hydroxy-3-methylantraquinone from *Hedyotis diffusa* Willd induces apoptosis via alteration of Fas/FasL and activation of caspase-8 in human leukemic THP-1 cells, *Arch. Med. Res.* **42**, 577-583.
- [51] L. Huang, H. Xu, T. Wu and G. Li (2021). *Hedyotis diffusa* Willd. suppresses hepatocellular carcinoma via downregulating AKT/mTOR pathways, *Evid. Based Complement. Altern. Med.* **2021**, 5210152.
- [52] Y. L. Li, J. Zhang, D. Min, Z. Hongyan, N. Lin and Q. S. Li (2016). Anticancer effects of 1,3-dihydroxy-2-methylantraquinone and the ethyl acetate fraction of *Hedyotis diffusa* Willd against HepG2 carcinoma cells mediated via apoptosis, *PLoS One* **11**, e0151502.
- [53] H. Chen, X. Shang, H. Yuan, Q. Niu, J. Chen, S. Luo, W. Li and X. Li (2022). Total flavonoids of *Oldenlandia diffusa* (Willd.) Roxb. suppresses the growth of hepatocellular carcinoma through endoplasmic reticulum stress-mediated autophagy and apoptosis, *Front. Pharmacol.* **13**, 1019670.

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- [54] X. Wang, J. Zhao, R. Zhang, X. Liu, C. Ma, G. Cao, Y. Wei and P. Yang (2022). Protective effect of *Hedyotis diffusa* Willd. ethanol extract on isoniazid-induced liver injury in the zebrafish model, *Drug Des. Devel. Ther.* **16**, 1995-2015.
- [55] Y. Y. Sunwoo, J. H. Lee, H. Y. Jung, Y. J. Jung, M. S. Park, Y. A. Chung, L. S. Maeng, Y. M. Han, H. S. Shin, J. Lee and S. I. Park (2015). *Oldenlandia diffusa* promotes antiproliferative and apoptotic effects in a rat hepatocellular carcinoma with liver cirrhosis, *Evid. Based Complement. Altern. Med.* **2015**, 501508.
- [56] X. Z. Chen, Z. Y. Cao, T. S. Chen, Y. Q. Zhang, Z. Z. Liu, Y. T. Su, L. M. Liao and J. Du (2012). Water extract of *Hedyotis diffusa* Willd suppresses proliferation of human HepG2 cells and potentiates the anticancer efficacy of low-dose 5-fluorouracil by inhibiting the CDK2-E2F1 pathway, *Oncol. Rep.* **28**, 742-748.
- [57] P. W. Yang, T. T. Chen, W. X. Zhao, G. W. Liu, X. J. Feng, S. M. Wang, Y. C. Pan, Q. Wang and S. H. Zhang (2021). *Scutellaria barbata* D.Don and *Oldenlandia diffusa* (Willd.) Roxb crude extracts inhibit hepatitis-B-virus-associated hepatocellular carcinoma growth through regulating circRNA expression, *J. Ethnopharmacol.* **275**, 114110.
- [58] Y. Shi, C. H. Wang and X. G. Gong (2008). Apoptosis-Inducing Effects of two anthraquinones from *Hedyotis diffusa* WILLD., *Biol. Pharm. Bull.* **31**, 1075-1078.
- [59] R. Wang, Z. Deng, Z. Zhu, J. Wang, X. Yang, M. Xu, X. Wang, Q. Tang, Q. Zhou, X. Wan, W. Wu and S. Wang (2023). Kaempferol promotes non-small cell lung cancer cell autophagy via restricting Met pathway, *Phytomedicine* **121**, 155090.
- [60] C. Wang, P. Xin, Y. Wang, X. Zhou, D. Wei, C. Deng and S. Sun (2018). Iridoids and sphingolipids from *Hedyotis diffusa*, *Fitoterapia* **124**, 152-159.
- [61] C. Sun, J. Yang, H. B. Cheng, W. X. Shen, Z. Q. Jiang, M. J. Wu, L. Li, W. T. Li, T. T. Chen, X. W. Rao, J. R. Zhou and M. H. Wu (2019). 2-hydroxy-3-methylanthraquinone inhibits lung carcinoma cells through modulation of IL-6-induced JAK2/STAT3 pathway, *Phytomedicine* **61**, 152848,
- [62] S. Wang, N. Yin, Y. Li, Z. Ma, W. Lin, L. Zhang, Y. Cui, J. Xia and L. Geng (2024). Molecular mechanism of the treatment of lung adenocarcinoma by *Hedyotis diffusa*: an integrative study with real-world clinical data and experimental validation, *Front. Pharmacol.* **15**, 1355531.
- [63] X. Su, Y. Li, M. Jiang, J. Zhu, C. Zheng, X. Chen, J. Zhou, Y. Li, W. Xiao and Y. Wang (2019). Systems pharmacology uncover the mechanism of anti-non-small cell lung cancer for *Hedyotis diffusa* Willd., *Biomed. Pharmacother.* **109**, 969-984.
- [64] F. Huang, J. Pang, L. Xu, W. Niu, Y. Zhang, S. Li and X. Li (2022). *Hedyotis diffusa* injection induces ferroptosis via the Bax/Bcl2/VDAC2/3 axis in lung adenocarcinoma, *Phytomedicine* **104**, 154319.
- [65] E. Dekker, P.J. Tanis, J. L. A. Vleugels, P. M. Kasi and M. B. Wallace (2019). Colorectal cancer, *Lancet* **394**, 1467-1480.
- [66] Z. Lai, Z. Yan, W. Chen, J. Peng, J. Feng, Q. Li, Y. Jin and J. Lin (2017). *Hedyotis diffusa* Willd suppresses metastasis in 5-fluorouracil-resistant colorectal cancer cells by regulating the TGF- $\beta$  signaling pathway, *Mol. Med. Rep.* **16**, 7752-7758.
- [67] J. Lin, Y. Chen, L. Wei, X. Chen, W. Xu, Z. Hong, T. J. Sferra and J. Peng (2010). *Hedyotis diffusa* Willd extract induces apoptosis via activation of the mitochondrion-dependent pathway in human colon carcinoma cells, *Int. J. Oncol.* **37**, 1331-1338.

- [68] J. Lin, Q. Li, H. Chen, H. Lin, Z. Lai and J. Peng (2015). *Hedyotis diffusa* Willd. extract suppresses proliferation and induces apoptosis via IL-6-inducible STAT3 pathway inactivation in human colorectal cancer cells, *Oncol. Lett.* **9**, 1962-1970.
- [69] J. Lin, L. Wei, A. Shen, Q. Cai, W. Xu, H. Li, Y. Zhan, Z. Hong and J. Peng (2013). *Hedyotis diffusa* Willd extract suppresses Sonic hedgehog signaling leading to the inhibition of colorectal cancer angiogenesis, *Int. J. Oncol.* **42**, 651-656.
- [70] Q. Cai, J. Lin, L. Wei, L. Zhang, L. Wang, Y. Zhan, J. Zeng, W. Xu, A. Shen, Z. Hong and J. Peng (2012). *Hedyotis diffusa* Willd inhibits colorectal cancer growth in vivo via inhibition of STAT3 signaling pathway, *Int. J. Mol. Sci.* **12**, 6117-6128.
- [71] D. Zhu, S. Yuan and C. Chen (2023). *Hedyotis diffusa*-*Scutellaria barbata* (HD-SB) suppresses the progression of colorectal cancer cells via the hsa circ 0039933/hsa-miR-204-5p/wnt11 axis. *Sci. Rep.* **13**, 13331.
- [72] Q. Li, X. Wang, A. Shen, Y. Zhang, Y. Chen, T. J. Sferra, J. Lin and J. Peng (2015). *Hedyotis diffusa* Willd overcomes 5-fluorouracil resistance in human colorectal cancer HCT-8/5-FU cells by downregulating the expression of P-glycoprotein and ATP-binding cassette subfamily G member 2, *Exp. Ther. Med.* **10**, 1845-1850.
- [73] W. Chen, Y. Jin, H. Yang, L. Wei and J. Lin (2018). *Hedyotis diffusa* Willd reduces migration and invasion through inhibition of TGF- $\beta$ -induced EMT in colorectal cancer cells, *Eur. J. Int. Med.* **23**, 57-63.
- [74] K. Kim, E. A. Shin, J. H. Jung, J. E. Park, D. S. Kim, B. S. Shim and S. H. Kim (2019). Ursolic acid induces apoptosis in colorectal cancer cells partially via upregulation of micro RNA-4500 and inhibition of JAK2/STAT3 phosphorylation, *Int. J. Mol. Sci.* **20**, 114.
- [75] Q. Li, Z. Lai, Z. Yan, J. Peng, Y. Jin, L. Wei and J. Lin (2018). *Hedyotis diffusa* Willd inhibits proliferation and induces apoptosis of 5-FU resistant colorectal cancer cells by regulating the PI3K/AKT signaling pathway, *Mol. Med. Rep.* **17**, 358-365.
- [76] Z. Wu, B. Yin and F. You (2022). Molecular mechanism of anti-colorectal cancer effect of *Hedyotis diffusa* Willd and its extracts, *Front. Pharmacol.* **13**, 820474.
- [77] J. Feng, Y. Jin, J. Peng, L. Wei, Q. Cai, Z. Yan, Z. Lai and J. Lin (2017). *Hedyotis diffusa* willd extract suppresses colorectal cancer growth through multiple cellular pathways. *Oncol. Lett.* **14**, 8197-8205.
- [78] T. W. Chung, H. Choi, J. M. Lee, S. H. Ha, C. H. Kwak, F. Abekura, J. Y. Park, Y. C. Chang, K. T. Ha, S. H. Cho, H. Wook Chang, Y. C. Lee and C. H. Kim (2017). Corrigendum to *Oldenlandia diffusa* suppresses metastatic potential through inhibiting matrix metalloproteinase-9 and intercellular adhesion molecule-1 expression via p38 and ERK1/2 MAPK pathways and induces apoptosis in human breast cancer MCF-7 cells, *J. Ethnopharmacol.* **195**, 309-317.
- [79] T. Fang, Y. X. Yan, Y. Yang, Y. X. Lv, Q. Q. Chang and D. D. Zhang (2020). Ethyl acetate fraction from *Hedyotis diffusa* plus *Scutellaria barbata* suppresses migration of bone-metastatic breast cancer cells via OPN-FAK/ERK/NF- $\kappa$ B axis, *Evid. Based Complement. Altern. Med.* **2020**, 3573240.
- [80] T. T. Ma, G. L. Zhang, C. F. Dai, B. R. Zhang, K. X. Cao, C. G. Wang, G. W. Yang and X. M. Wang (2020). *Scutellaria barbata* and *Hedyotis diffusa* herb pair for breast cancer treatment: Potential mechanism based on network pharmacology, *J. Ethnopharmacol.* **259**, 112929.
- [81] Z. Liu, M. Liu, M. Liu and J. Li (2010). Methylantraquinone from *Hedyotis diffusa* WILLD induces Ca<sup>2+</sup>-mediated apoptosis in human breast cancer cells, *Toxicol. in Vitro* **24**, 142-147.

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- [82] G. G. L. Yue, J. K. M. Lee, B. C. L. Chan, H. F. Kwok, S. W. H. Hoi, D. M. Y. Sze, K. P. Fung, P. C. Leung and C. B. S. Lau (2018). An innovative anti-cancer Chinese herbal formula exhibited multi-targeted efficacies in metastatic breast cancer mouse model, *Chin. Med.* **13**, 64.
- [83] Y. Zhang, R. F. Xie, Q. G. Xiao, R. Li, X. L. Shen and X. G. Zhu (2014). *Hedyotis diffusa* Willd extract inhibits the growth of human glioblastoma cells by inducing mitochondrial apoptosis via AKT/ERK pathways, *J. Ethnopharmacol.* **158**, 404-411.
- [84] S. J. Song, X. Liu, Q. Ji, D. Z. Sun, L. J. Xiu, J. Y. Xu and X. Q. Yue (2022). Ziyin Huatan Recipe, a Chinese herbal compound, inhibits migration and invasion of gastric cancer by upregulating RUNX3 expression, *J. Integr. Med.* **20**, 355-364.
- [85] L. Ou, M. Li and Y. Hou (2024). Network pharmacology, bioinformatics, and experimental validation to identify the role of *Hedyotis diffusa* willd against gastric cancer through the activation of the endoplasmic reticulum stress, *Heliyon* **10**, e28833.
- [86] H. Jin and M. Cui (2022). Recognition of potential therapeutic role of 2-hydroxy-3-methylanthraquinones in the treatment of gallbladder carcinoma: a proteomics analysis, *Fundam. Clin. Pharmacol.* **36**, 350-362.
- [87] Y. Song, H. Wang, Y. Pan and T. Liu (2019). Investigating the multi-target pharmacological mechanism of *Hedyotis diffusa* Willd acting on prostate cancer: a network pharmacology approach, *Biomolecules* **9**, 591.
- [88] S. S. T. Hnit, M. Yao, C. Xie, G. Ge, L. Bi, S. Jin, L. Jiao, L. Xu, L. Long, H. Nie, Y. Jin, L. Rogers, N. Suchowerska, M. Wong, T. Liu, P. De Souza, Z. Li and Q. Dong (2020). Transcriptional regulation of G2/M regulatory proteins and perturbation of G2/M Cell cycle transition by a traditional Chinese medicine recipe, *J. Ethnopharmacol.* **251**, 112526.
- [89] L. T. Pan, Y. Sheung, W. P. Guo, Z. B. Rong and Z. M. Cai (2016). *Hedyotis diffusa* plus *Scutellaria barbata* induce bladder cancer cell apoptosis by inhibiting Akt signaling pathway through downregulating miR-155 expression, *Evi. Based Complement. Altern. Med.* **2016**, 9174903.
- [90] Y. H. Song, S. J. Jeong, H. Y. Kwon, B. Kim, S. H. Kim and D. Y. Yoo (2012). Ursolic acid from *Oldenlandia diffusa* induces apoptosis via activation of caspases and phosphorylation of glycogen synthase kinase 3 beta in SK-OV-3 ovarian cancer cells, *Biol. Pharm. Bull.* **35**, 1022-1028.
- [91] X. Xu, F. Chen, L. Zhang, L. Liu, C. Zhang, Z. Zhang and W. Li (2021). Exploring the mechanisms of anti-ovarian cancer of *Hedyotis diffusa* Willd and *Scutellaria barbata* D. Don through focal adhesion pathway, *J. Ethnopharmacol.* **279**, 114343.
- [92] L. Zhang, J. Zhang, B. Qi, G. Jiang, J. Liu, P. Zhang, Y. Ma and W. Li (2016). The anti-tumor effect and bioactive phytochemicals of *Hedyotis diffusa* willd on ovarian cancer cells, *J. Ethnopharmacol.* **192**, 132-139.
- [93] Y. K. Lee, J. Lim, S. Y. Yoon, J. C. Joo, S. J. Park and Y. J. Park (2019). Promotion of cell death in cisplatin-resistant ovarian cancer cells through KDM1B-DCLRE1B modulation, *Int. J. Mol. Sci.* **20**, 2443.
- [94] C. Y. Wang, T. C. Wang, W. M. Liang, C. H. Hung, J. S. Chiou, C. J. Chen, F. J. Tsai, S. T. Huang, T. Y. Chang, T. H. Lin, C. C. Liao, S. M. Huang, T. M. Li and Y. J. Lin (2021). Effect of Chinese herbal medicine therapy on overall and cancer related mortality in patients with advanced nasopharyngeal carcinoma in Taiwan, *Front. Pharmacol.* **11**, 607413.

- [95] C. Wu, H. Luo, W. Ma, X. Ren, C. Lu, N. Li and Z. Wang (2017). Polysaccharides isolated from *Hedyotis diffusa* inhibits the aggressive phenotypes of laryngeal squamous carcinoma cells via inhibition of Bcl-2, MMP-2, and  $\mu$ PA, *Gene* **637**, 124-129.
- [96] C. Ye, B. Zhang, Z. Tang, C. Zheng, Q. Wang and X. Tong (2024). Synergistic action of *Hedyotis diffusa* Willd and *andrographis paniculata* in nasopharyngeal carcinoma: downregulating AKT1 and upregulating VEGFA to curb tumorigenesis, *Int. Immunopharmacol.* **132**, 111866.
- [97] K. Qian, D. Fu, B. Jiang, Y. Wang, F. Tian, L. Song and L. Li (2021). Mechanism of *Hedyotis diffusa* in the treatment of cervical cancer, *Front. Pharmacol.* **12**, 808144.
- [98] P. Zhang, B. Zhang, J. Gu, L. Hao, F. Hu and C. Han (2015). The study of the effect of *Hedyotis diffusa* on the proliferation and the apoptosis of the cervical tumor in nude mouse model, *Cell Biochem. Biophys.* **72**, 783-789.
- [99] W. Ning, N. Xu, C. Zhou, L. Zou, J. Quan, H. Yang, Z. Lu, H. Cao and J. Liu (2022). Ethyl acetate fraction of *Hedyotis diffusa* Willd induces apoptosis via JNK/Nur77 pathway in hepatocellular carcinoma cells, *Evi. Based Complement. Altern. Med.* **2022**, 1932777.
- [100] W. L. Ma, N. Chang, Y. Yu, Y. T. Su, G. Y. Chen, W. C. Cheng, Y. C. Wu, C. C. Li, W. C. Chang and J. C. Yang (2022). Ursolic acid silences CYP19A1/aromatase to suppress gastric cancer growth, *Cancer Med.* **11**, 2824-2835.
- [101] D. Jing, X. Chen, Z. Zhang, F. Chen, F. Huang, Z. Zhang, W. Wu, Z. Shao and F. Pu (2023). 2-Hydroxy-3-methylantraquinone inhibits homologous recombination repair in osteosarcoma through the MYC-CHK1-RAD51 axis, *Molecular Med.* **29**, 15.
- [102] C. Ma, Y. Wei, Q. Liu, Y. Xin, G. Cao, X. Wang and P. Yang (2019). Polysaccharides from *Hedyotis diffusa* enhance the antitumor activities of cytokine-induced killer cells, *Biomed. pharmacother.* **117**, 109167.
- [103] H. Li, Z. Lai, H. Yang, J. Peng, Y. Chen and J. Lin (2019). *Hedyotis diffusa* Willd. inhibits VEGF-C-mediated lymphangiogenesis in colorectal cancer via multiple signaling pathways, *Oncol. Rep.* **42**, 1225-1236.
- [104] Z. Yan, J. Feng, J. Peng, Z. Lai, L. Zhang, Y. Jin, H. Yang, W. Chen and J. Lin (2017). Chloroform extract of *Hedyotis diffusa* Willd inhibits viability of human colorectal cancer cells via suppression of AKT and ERK signaling pathways, *Oncol. Lett.* **14**, 7923-7930.
- [105] P. W. Yang, P. L. Xu, C. S. Cheng, J. Y. Jiao, Y. Wu, S. Dong, J. Xie and X. Y. Zhu (2022). Integrating network pharmacology and experimental models to investigate the efficacy of QYHJ on pancreatic cancer, *J. Ethnopharmacol.* **297**, 115516,
- [106] Y. X. Lv, H. R. Pan, X. Y. Song, Q. Q. Chang, D. D. Zhang (2021). *Hedyotis diffusa* plus *Scutellaria barbata* suppress the growth of non-small-cell lung cancer via NLRP3/NF- $\kappa$ B/MAPK signaling pathways, *Evi. Based Complement. Altern. Med.* **2021**, 6666499.
- [107] J. Lin, L. Wei, W. Xu, Z. Hong, X. Liu and J. Peng (2011). Effect of *Hedyotis diffusa* Willd extract on tumor angiogenesis, *Mol. Med. Rep.* **4**, 1283-1288.
- [108] L. Lu, S. Zhan, X. Liu, X. Zhao, X. Lin and H. Xu (2020). Antitumor effects and the compatibility mechanisms of herb pair *Scleromitron diffusum* (Willd.) R. J. Wang–*Sculellaria barbata* D. Don, *Front. Pharmacol.* **11**, 292.
- [109] Y. L. Li, X. Chen, S. Q. Niu, H. Y. Zhou and Q. S. Li (2020). Protective antioxidant effects of amentoflavone and total flavonoids from *Hedyotis diffusa* on H<sub>2</sub>O<sub>2</sub>-Induced HL-O<sub>2</sub> cells through ASK1/p38 MAPK pathway, *Chem. Biodivers.* **17**, e2000251.

- [110] S. Ji, A. Fattahi, N. Raffel, I. Hoffmann, M.W. Beckmann, R. Dittrich and M. Schrauder (2017). Antioxidant effect of aqueous extract of four plants with therapeutic potential on gynecological diseases; *Semen persicae*, *Leonurus cardiaca*, *Hedyotis diffusa*, and *Curcuma zedoaria*, *Eur. J. Med. Res.* **22**, 50.
- [111] P. Wang, Y. Wang, T. Feng, Z. Yan, D. Zhu, H. Lin, M. Iqbal, D. Deng, M. F. Kulyar and Y. Shen (2023). *Hedyotis diffusa* alleviate aflatoxin B1-induced liver injury in ducks by mediating Nrf2 signaling pathway, *Ecotoxicol. Environ. Saf.* **249**, 114339.
- [112] M. Dai, F. Wang, Z. Zou, G. Xiao, H. Chen and H. Yang (2017). Metabolic regulations of a decoction of *Hedyotis diffusa* in acute liver injury of mouse models. *Chin. Med.* **12**, 35.
- [113] D. H. Chen, P. J. Mao, W. J. Diao and Q. Li (2024). Toxicity study of compound granules of *Hedyotis diffusa*: Acute toxicity and long-term toxicity, *J. Ethnopharmacol.* **321**, 117434.
- [114] C. Lou, C. Lin, W. Wang, H. Jiang, T. Cai, S. Lin, X. Xue, J. Lin and X. Pan (2023). Extracts of *Oldenlandia diffusa* protects chondrocytes via inhibiting apoptosis and associated inflammatory response in osteoarthritis, *J. Ethnopharmacol.* 316, 116744.
- [115] H. Zhu, Q. H. Liang, X. G. Xiong, Y. Wang, Z. H. Zhang, M. J. Sun, X. Lu and D. Wu (2018). Anti-inflammatory effects of p-Coumaric acid, a natural compound of *Oldenlandia diffusa*, on arthritis model rats, *Evi. Based Complement. Altern. Med.* **2018**, 5198594.
- [116] Y. Li, T. Ding, J. Chen, J. Ji, W. Wang, B. Ding, W. Ge, Y. Fan and L. Xu (2022). The protective capability of *Hedyotis diffusa* Willd on lupus nephritis by attenuating the IL-17 expression in MRL/lpr mice, *Front. Immunol.* **13**, 943827.
- [117] L. Xu, Y. Li, J. Ji, Y. Lai, J. Chen, T. Ding, H. Li, B. Ding and W. Ge (2022). The anti-inflammatory effects of *Hedyotis diffusa* Willd on SLE with STAT3 as a key target, *J. Ethnopharmacol.* **298**, 115597.
- [118] J. Wang, B. Shi, Y. Pan, Z. Yang, W. Zou and M. Liu (2023). Asperulosidic acid ameliorates renal interstitial fibrosis via removing indoxyl sulfate by up-regulating organic anion transporters in a unilateral ureteral obstruction mice model, *Molecules* **28**, 7690.
- [119] J. H. Ye, M. H. Liu, X. L. Zhang and J. Y. He (2015). Chemical profiles and protective effect of *Hedyotis diffusa* Willd in lipopolysaccharide-induced renal inflammation mice, *Int. J. Mol. Sci.* **16**, 27252-27269.
- [120] Y. Chen, Y. Lin, Y. Li and C. Li (2016). Total flavonoids of *Hedyotis diffusa* Willd inhibit inflammatory responses in LPS-activated macrophages via suppression of the NF- $\kappa$ B and MAPK signaling pathways, *Exp. Ther. Med.* **11**, 1116-1122.
- [121] P. Jia, W. Liu, S. Liu and W. Gao (2018). Therapeutic effects of *Hedyotis diffusa* Willd. on type II collagen-induced rheumatoid arthritis in rats, *Chinese J. Appl. Physiol.* **34**, 558-561.
- [122] R. Liu, P. Wang, C. Wu, J. Chen, C. Li, Y. Xie, Q. Wang, J. Liu, H. He and J. Zhu (2018). Therapeutic effects of *Hedyotis diffusa* Willd in a COPD mouse model challenged with LPS and smoke, *Exp. Ther. Med.* **15**, 3385-3391.
- [123] L. F. Qin, H. H. Gao, X. Zhang, X. Yuan, Z. M. Feng, P. C. Zhang, J. S. Jiang and Y. N. Yang (2024). Seventeen undescribed iridoid derivatives with anti-inflammatory effects from *Hedyotis diffusa* and their structure-activity relationships, *Phytochemistry* **217**, 113904.
- [124] J. H. Park and W. K. Whang (2020). Bioassay-guided isolation of anti-alzheimer active components from the aerial parts of *Hedyotis diffusa* and *Simultaneous* analysis for marker compounds, *Molecules* **25**, 5867.

- [125] J. Li, G. Yang, W. Shi, X. Fang, L. Han and Y. Cao (2022). Anti-Alzheimer's disease active components screened out and identified from *Hedyotis diffusa* combining bioaffinity ultrafiltration LC-MS with acetylcholinesterase, *J. Ethnopharmacol.* **296**, 115460.
- [126] J. E. Lee, H. S. Song, M. N. Park, S. H. Kim, B. S. Shim and B. Kim (2018). Ethanol extract of *Oldenlandia diffusa* herba attenuates scopolamine-induced cognitive impairments in mice via activation of BDNF, P-CREB and inhibition of acetylcholinesterase, *Int. J. Mol. Sci.* **19**, 363.
- [127] T. Wajima, Y. Anzai, T. Yamada, H. Ikoshi, N. Noguchi (2016). *Oldenlandia diffusa* extract inhibits biofilm formation by haemophilus influenzae clinical isolates, *PoLS. One.* **11**, e0167335.
- [128] P. Malfertheiner, M. C. Camargo, E. El-Omar, J. M. Liou, R. Peek, C. Schulz, S. I. Smith and S. Suerbaum (2023). Helicobacter pylori infection, *Nat. Rev. Dis. Primers* **9**, 19.
- [129] F. Liu, X. Nong, W. Qu and X. Li (2023). Weikangling capsules combined with omeprazole ameliorates ethanol-induced chronic gastritis by regulating gut microbiota and EGF-EGFR-ERK pathway, *Life Sci.* **315**, 121368.
- [130] J. J. Y (2023). Clinical observation of gastric Fukang Fang in treating patients with (damp-heat evidence) Hp-related chronic gastritis with enteritis, *Guangxi Univ. Trad. Chinese Medicin.* **1**, 1-87.
- [131] R. Y. Ji (2022). Clinical observation on the treatment of chronic atrophic gastritis by Qi Ling Fang and the effect on the expression of gastric mucosal oncogenes p53 and MDM2, *Nanjing Univ. Trad. Chinese Medicin.* **1**, 1-47.
- [132] Y. Z. Wu (2019). Clinical observation on the treatment of spleen and stomach damp-heat type chronic atrophic gastritis by adding and subtracting Lizhong Fuyuan Fang, *Shanghai Univ. Trad. Chinese Medicin.* **1**, 1-68.
- [133] N. L. Zhang (2021). Clinical observation on the treatment of chronic atrophic gastritis by resolving turbidity, detoxifying and activating blood formula and research on NF- $\kappa$ B signaling pathway, *Hebei College Trad. Chinese Medicin.* **1**, 1-126.
- [134] Q. X. Chen (2022).. Clinical observation on the adjuvant treatment of HP-infected carcass yin (chronic gastro-sinusitis) with the Zhuang medicine prescription gastric toxin clear, *Guangxi Univ. Trad. Chinese Medicin.* **1**, 1-89.
- [135] Y. Shi, X. Shi, M. Zhao, S. Ma and Y. Zhang (2024). Pharmacological potential of *Astragali Radix* for the treatment of kidney diseases, *Phytomedicine* **123**, 155196.
- [136] F. Q. Jiang (2023). Clinical observation on the treatment of spleen and kidney qi deficiency and damp-heat type chronic nephritis by Yiqi Qingli Fang, *Shandong Univ. Trad. Chinese Medicin.* **1**, 1-46.
- [137] L. X. Yu (2021). Clinical observation on the treatment of proteinuria in chronic glomerulonephritis of qi and yin deficiency and dampness-heat internalization type by Huimin Combination, *Heilongjiang Academy Trad. Chinese Medicin.* **1**, 1-39.
- [138] J. J. Lu (2021). Clinical observation on the treatment of chronic glomerulonephritis with spleen-kidney qi deficiency and stasis type by yi kidney, strengthen spleen and Tongluo Formula, *Fujian Univ. Traditional Chinese Medicine* **1**, 1-51.
- [139] J. Z. Wu (2012). Clinical observation and animal experiments of yi kidney qingli granules intervening in chronic glomerulonephritis with renal deficiency and damp-heat syndrome, *Nanjing Univ. Trad. Chinese Medicin.* **1**, 1-55.
- [140] H. W. Ge (2021). Clinical observation on the treatment of proteinuria in chronic nephritis by combining the method of benefiting qi, dispelling wind, resolving blood stasis and clearing profits with Lei Gongtou Polyglucoside Tablets, *Nanjing Univ. Trad. Chinese Medicin.* **1**, 1-44.

- [141] Z. Y. Li (2011). Clinical observation and experimental study on the treatment of chronic hepatitis B by qi tonification and detoxification, *Guangzhou Univ. Trad. Chinese Medicin.* **1**, 1-73.
- [142] F. Kong (2018). Clinical observation on early intervention of Hashimoto's thyroiditis by liver-sparing, spleen-strengthening and detoxification formula, *Shandong Univ. Trad. Chinese Medicin.* **1**, 1-43.
- [143] Q. H. Gao (2022). Clinical observation on the treatment of type III prostatitis by Gui Huang Fang and experimental study on the regulation of NLRP3-mediated cellular focal death, *China Acad. Trad. Chinese Medicin.* **1**, 1-121.
- [144] J. J. Wu, A. Kavanaugh, M. G. Lebwohl, R. Gniadecki and J. F. Merola (2022). Psoriasis and metabolic syndrome: implications for the management and treatment of psoriasis, *J. Eur. Acad. Dermatol. Venereol.* **36**, 797-806.
- [145] S. Meng, Z. Lin, Y. Wang, Z. Wang, P. Li and Y. Zheng (2018). Psoriasis therapy by Chinese medicine and modern agents, *Chin. Med.* **13**, 16.
- [146] H. H. Ma (2019). Clinical observation on the treatment of blood-heat and wind-abundant type psoriasis by Ke Yin eliminating spots No.1 formula, *Shanxi Univ. Trad. Chinese Medicin.* **1**, 1-30.
- [147] Q. Zhang (2021). Clinical observation on the treatment of plaque-type psoriasis with blood stasis by activating blood circulation and dissipating blood stasis and eliminating silver soup, *Hebei North College* **1**, 1-54.
- [148] Y. P. An (2013). Clinical observation on the treatment of blood-heat syndrome of psoriasis of common type with the addition and subtraction of anti-yin 1, *Heilongjiang Univ. Trad. Chinese Medicin.* **1**, 1-93.
- [149] J. Gui (2013). Clinical observation on 95 cases of psoriasis treated with blood-heat syndrome, *Beijing Univ. Trad. Chinese Medicin.* **1**, 1-50.
- [150] A. L. Zaenglein (2018). Acne vulgaris, *N. Engl. J. Med.* **379**, 1343-1352,
- [151] C. Y. Chen, G. Y. Xu, Y. Y. Shang, M. S. Xu and P. Liu (2021). Acupuncture: a therapeutic approach against acne, *J. Cosmet. Dermatol.* **20**, 3829-3838.
- [152] B. Yu, N. N. Diao, Y. Zhang, X. Z. Li, N. Yu, Y. F. Ding and Y. L. Shi (2020). Network pharmacology-based identification for therapeutic mechanisms of Dangguikushen pill in acne vulgaris, *Dermatol. Ther.* **33**, e14061.
- [153] H. L. Zhang (2010). Clinical observation of cooling blood and removing toxins pill in the treatment of common acne, *Heilongjiang Univ. Trad. Chinese Medicin.* **1**, 1-59.
- [154] X. Y. Zheng (2017). Clinical observation on the treatment of lung meridian wind-heat type of acne vulgaris with the addition and subtraction formula of loquat lung-clearing drink, *Nanjing Univ. Trad. Chinese Medicin.* **1**, 1-41.
- [155] H. Gao (2012). Clinical observation of Ke acne soup in the treatment of common acne (phlegm-dampness stagnation type), *Heilongjiang Univ. Trad. Chinese Medicin.* **1**, 1-51.
- [156] Z. C. Lin (2017). Clinical observation on the treatment of spleen deficiency and dampness acne by adding flavor and warm gallbladder soup, *Heilongjiang Univ. Trad. Chinese Medicin.* **1**, 1-37.
- [157] J. L. Liu (2014) Clinical observation on the treatment of adolescent acne and its effect on the quality of life by clearing the lung and calming the liver, *Guangzhou Univ. Trad. Chinese Medicin.* **1**, 1-47.
- [158] R. J. Rebello, C. Oing, K. E. Knudsen, S. Loeb, D. C. Johnson, R. E. Reiter, S. Gillissen, T. Van der Kwast and R. G. Bristow (2021). Prostate cancer, *Nat. Rev. Dis. Primers* **7**, 9.
- [159] C. J. Halbrook, C. A. Lyssiotis, M. Pasca di Magliano and A. Maitra (2023). Pancreatic cancer: advances and challenges, *Cell* **186**, 1729-1754.

- [160] S. H. Liu, P. S. Chen, C. C. Huang, Y. T. Hung, M. Y. Lee, W. H. Lin, Y. C. Lin and A. Y. L. Lee (2021). Unlocking the mystery of the therapeutic effects of Chinese medicine on cancer, *Front. Pharmacol.* **11**, 601785.
- [161] Q. Ji, Y. Q. Luo, W. H. Wang, X. Liu, Q. Li and S. B. Su (2016). Research advances in traditional Chinese medicine syndromes in cancer patients, *J. Integrat. Med.* **14**, 12-21.
- [162] Y. H. Liao, C. I. Li, C. C. Lin, J. G. Lin, J. H. Chiang and T. C. Li (2017). Traditional Chinese medicine as adjunctive therapy improves the long-term survival of lung cancer patients, *J. Cancer Res. Clin. Oncol.* **143**, 2425-2435.
- [163] X. Li (2018). Clinical observation and animal experimental study of Bai hua she she cao injection for the treatment of colorectal cancer, *Shandong Univ. Trad. Chinese Medicin.* **1**, 1-50.
- [164] X. X. Liu (2019). Clinical observation and experimental study of Ci Half Combination in the treatment of non-gene mutated advanced lung adenocarcinoma (Yin deficiency and heat toxicity type), *Shandong Univ. Trad. Chinese Medicin.* **1**, 1-50.
- [165] X. Y. Wang (2021). Clinical observation on the treatment of advanced non-small cell lung cancer with qi and yin deficiency type by ginseng astragalus and lung benefit soup, *Shandong Univ. Trad. Chinese Medicin.* **1**, 1-43.
- [166] A. S. Wang (2020). Clinical observation on the treatment of advanced NSCLC by adding flavored astragalus and lotus combination and research on anti-tumor immune mechanism of Huang qi methyl glycoside, *Shandong Univ. Trad. Chinese Medicin.* **1**, 1-79.
- [167] Q. Wang (2016). Clinical observation of spleen-strengthening and detoxification formula combined with chemotherapy in the treatment of gastric cancer after surgery, *Nanjing Univ. Trad. Chinese Medicin.* **1**, 1-44.
- [168] D. S. J. Wang and L. Qi (2014). Nomenclature clarification of the traditional Chinese medicine Baihuasheshcao and its adulterants based on molecular and morphological evidence, *J. Trop. Subtrop.* **22**, 431-442.
- [169] Y. Cheng, S. Tang, Y. Guo and T. Ye (2018). Total synthesis of anti-tuberculosis natural products ilamycins E1 and F, *Org. Lett.* **20**, 6166-6169.
- [170] J. Wang, Z. K. Zhang, F. F. Jiang, B. W. Qi, N. Ding, S. Y. Y. Hnin, X. Liu, J. Li, X. H. Wang, P. F. Tu, I. Abe, H. Morita and S. P. Shi (2020). Deciphering the biosynthetic mechanism of pelletierine in lycopodium alkaloid biosynthesis, *Org. Lett.* **22**, 8725-8729.
- [171] L. Pinzi and G. Rastelli (2019). Molecular docking: shifting paradigms in drug discovery, *Int. J. Mol. Sci.* **20**, 4331.
- [172] E. H. Liu, T. Zhou, G. B. Li, J. Li, X. N. Huang, F. Pan and N. Gao (2012). Characterization and identification of iridoid glucosides, flavonoids and anthraquinones in *Hedyotis diffusa* by high-performance liquid chromatography/electrospray ionization tandem mass spectrometry, *J. Sep. Sci.* **35**, 263-272.
- [173] Y. Y. Zhang and J. B. Luo (2008). Studies on the chemical constituents in herb of *Hedyotis diffusa*, *Zhong Yao Cai* **31**, 522-524.
- [174] J. Wu, Z. J. Ye, L. J. Yu, X. Q. and Chen (2023). Two new iridoid glycosides from *Hedyotis diffusa*, *J. Asian Nat. Prod. Res.* **25**, 27-35.
- [175] C. Li, X. Xue, D. Zhou, F. Zhang, Q. Xu, L. Ren and X. Liang (2008). Analysis of iridoid glucosides in *Hedyotis diffusa* by high-performance liquid chromatography/electrospray ionization tandem mass spectrometry, *J. Pharm. Bio. Anal.* **48**, 205-211.

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- [176] Y. Nishihama, K. Masuda, M. Yamaki, S. Takagi and K. Sakina (1981). Three new iridoid glucosides from *Hedyotis diffusa*, *Planta Med.* **43**, 28-33.
- [177] Y. Zhang, Y. Chen, C. Fan, W. Ye and J. Luo (2010). Two new iridoid glucosides from *Hedyotis diffusa*, *Fitoterapia* **81**, 515-517.
- [178] Y. Zhang, H. Hu and J. Luo (2020). Diffusosides C and D, two new iridoid glucosides from *Oldenlandia diffusa*, *Nat. Prod. Res.* **36**, 2300-2305.
- [179] Z. Liang, M. He, W. Fong, Z. Jiang and Z. Zhao (2008). A comparable, chemical and pharmacological analysis of the traditional Chinese medicinal herbs *Oldenlandia diffusa* and *O. corymbosa* and a new valuation of their biological potential, *Phytomedicine* **15**, 259-267.
- [180] H. Wu, X. Tao, Q. Chen and X. Lao (1991). Iridoids from *Hedyotis diffusa*, *J. Nat. Prod.* **54**, 254-256.
- [181] Q. M. Zhang and Z. Y. Sun (2014). Study on Chemical Constituents of *Oldenlandia diffusa*, *Zhong Yao Cai* **37**, 2216-2218.
- [182] C. Li, Y. Zhao, Z. Guo, X. Zhang, X. Xue and X. Liang (2014). Effective 2D-RPLC/RPLC enrichment and separation of micro-components from *Hedyotis diffusa* Willd. and characterization by using ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry, *J. Pharm. Biomed. Anal.* **99**, 35-44.
- [183] Y. B. Yang, X. Q. Yang and Z. T. Ding (2007). Chemical constituents from *Hedyotis diffusa*, *Chin. J. Yunnan Univ.* **2**, 187-189+212.
- [184] Y. J. Zhou, K. S. Wu, G. R. Zeng, J. B. Tan, K. P. Xu, F. S. Li and G. S. Tan (2007). Study on chemical constituents of *Oldenlandia diffusa*, *Chin. J. Chin. Mater. Med.* **7**, 590-593.
- [185] H. Zhang, Y. Chen and R. Huang (2005). Study on flavonoids from *Hedyotis diffusa* Willd, *Zhong yao cai* **28**, 385-387.
- [186] C. M. Lu, J. J. Yang, P. Y. Wang and C. C. Lin (2000). A new acylated flavonol glycoside and antioxidant effects of *Hedyotis diffusa*, *Planta Med.* **66**, 374-377.
- [187] L. Wang, C. Zhou and H. Z. Mai (2003). Analysis of volatile compounds in *Hedyotis diffusa* and *Hedyotis corymbosa*, *J. Chin. Mater. Med.* **26**, 563-564.
- [188] Y. Kim, E. J. Park, J. Kim, Y. Kim, S. R. Kim and Y. Y. Kim (2001). Neuroprotective constituents from *Hedyotis diffusa*, *J. Nat. Prod.* **64**, 75-78.
- [189] F. Z. Ren, G. S. Liu, L. Zhang and G. Y. Niu (2005). Studies on chemical constituents of *Hedyotis diffusa* Willd, *J. Chin. Pharm. Sci.* **40**, 502-504.
- [190] W. H. Huang, Y. B. Li and J. Q. Jiang (2008). Chemical constituents from *Hedyotis diffusa*, *China J. Chin. Mater. Med.* **33**, 524-526.
- [191] Q. X. Meng, R. H. Roubin and J. R. Hanrahan (2013), Ethnopharmacological and bioactivity guided investigation of five TCM anticancer herbs, *J. Ethnopharmacol.* **148**, 229-238.
- [192] X. D. Kang, X. Li, Y. Mao, C. C. Zhao, N. Li and D. L. Meng (2007). Chemical constituents of *Hedyotis diffusa* Willd, *J. Shenyang Pharm. Univ.* **24**, 479-481.
- [193] Y. Q. Liu, W. J. Yin, Y. Liu, Y. N. Feng and Q. T. Lv (2014). Summarization on the chemical constituents of *Oldenlandia Diffusa* Willd., *Shandong J. Tradit. Chin. Med.* **33**, 709-712.
- [194] Y. Shi, C. H. Wang and X. G. Gong (2008). Apoptosis-inducing effects of two anthraquinones from *Hedyotis diffusa* WILLD, *Biol. Pharm. Bull.* **31**, 1075-1078.
- [195] W. H. Huang, S. H. Yu, Y. B. Li and J. Q. Jiang (2008). Two new anthraquinones from *Hedyotis diffusa*, *J. Asian Nat. Prod. Res.* **10**, 467-471.

- [196] X. D. Kang, X. Li, C. C. Zhao and Y. Mao (2008). Two new anthraquinones from *Hedyotis diffusa* W, *J. Asian Nat. Prod. Res.* **10**, 193-197.
- [197] X. D. Kang, X. Li and Y. Mao (2006). A new anthraquinone from *Hedyotis diffusa* Willd, *Chin. J. Med. Chem.* **16**, 368.
- [198] Y. Li, J. M. Li, Z. Jiang and X. J. Jiang (2008). A new anthraquinone from *Hedyotis diffusa*, *Chin. J. Med. Chem.* **4**, 298-299.
- [199] Y. F. Dai, Y. M. Lin and F. C. Chen (1979). Components of *Hedyotis diffusa* Willd, *Chem.* **3**, 60-61.
- [200] T. I. Ho, G. P. Chen, Y. C. Lin, Y. M. Lin and F. C. Chen (1986). An anthraquinone from *Hedyotis diffusa*, *Phytochemistry* **25**, 1988-1989.
- [201] X. Yang, L. Chen, C. Liu, Y. Qin, Y. Tang and S. Li (2017). Rapid screening, separation, and detection of  $\alpha$ -glucosidase inhibitors from *Hedyotis diffusa* by ultrafiltration–liquid chromatography tandem mass spectrometry–high-speed countercurrent chromatography, *Med. Chem. Res.* **26**, 3315-3322.
- [202] W. H. Huang, Y. B. Li, and J. Q. Jiang (2008). Chemical constituents from *Hedyotis diffusa*, *China J. Chin. Mater. Med.* **34**, 712-714.
- [203] L. Wang, C. Zhou and H. Z. Mai (2003). Analysis of volatile compounds in *Hedyotis diffusa* and *Hedyotis corymbosa*, *J. Chin. Mater. Med.* **8**, 563-564,
- [204] S. Yang, W. W. Yang, J. F. Hu, Q. T. Lv and R. Rong (2012). GC-MS Combined with kovats index analysis for volatile compounds in *Hedyoti diffusa*, *Chin. J. Exper. Tradit. Med. Formul.* **18**, 93-95.
- [205] Y. O. Son, S. H. Kook and J. C. Lee (2017). Glycoproteins and polysaccharides are the main class of active constituents required for lymphocyte stimulation and antigen-specific immune response induction by traditional medicinal herbal plants, *J. Med. Food* **20**, 1011-1021.
- [206] M. Li, R. W. Jiang, P. M. Hon, L. Cheng, L. L. Li, J. R. Zhou, P. C. Shaw and P. P. H. But (2010). Authentication of the anti-tumor herb Baihuasheshcao with bioactive marker compounds and molecular sequences, *Food Chem.* **119**, 1239-1245.
- [207] T. Ning, W. Shuang, Y. Ya and T. Fang (2002). Anticancer activity and principles of *Hedyotis diffusa*, *Nat. Prod. Res. Dev.* **14**, 33-36.
- [208] Y. Xu, X. X. Chen, Y. X. Jiang and D. D. Zhang (2018). Ethyl acetate fraction from *Hedyotis diffusa* plus *Scutellaria barbata* exerts anti-inflammatory effects by regulating miR-155 expression and JNK signaling pathway, *Evi. Based Complement. Altern. Med.* **2018**, 3593408.
- [209] J. Tan, L. Li, W. Shi, D. Sun, C. Xu, Y. Miao, H. Fan, J. Liu, H. Cheng, M. Wu and W. Shen (2018). Protective effect of 2-hydroxymethyl anthraquinone from *Hedyotis diffusa* Willd in lipopolysaccharide-induced acute lung injury mediated by TLR4-NF- $\kappa$ B pathway, *Inflammation* **41**, 2136-2148.
- [210] S. J. Kim, W. S. Chung, S. S. Kim, S. G. Ko and J. Y. Um (2011). Antiinflammatory effect of *Oldenlandia diffusa* and its constituent, hentriacontane, through suppression of caspase-1 activation in mouse peritoneal macrophages, *Phytother. Res.* **25**, 1537-1546.