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Phytochemistry, Pharmacology and Clinical Applications of *Cortex Daphnes*:A Review

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Abstracts: *Cortex Daphnes,* a traditional Chinese medicine, has been utilized in China for millennia owing to it's anti-inflammatory and analgesic properties. As it is belonging to the *Thymelaeaceae* family within the genus *Daphne*, it has traditionally been employed to dispel wind, eliminate dampness, alleviate pain, and dissipate blood stasis. Consequently, numerous scholars both domestically and internationally have investigated it's chemical composition, pharmacological effects, and various other aspectsAmong these, daphnetin stands out as the primary active constituent in *C. Daphnes*, holding significant value as a precursor molecule for drug development. Pharmacological research has demonstrated that compounds and extracts derived from *C. Daphnes* exhibit notable activities, including anti-inflammatory, anti-tumor, antibacterial, immunomodulatory, antioxidant, and analgesic effects. Clinically, *C. Daphnes* has a long-standing history of use in the treatment of rheumatic diseases. This presents considerable potential for further development and exploration. According to existing records, *C. Daphnes* exhibits low toxicity; therefore, refining its processing technology, conducting toxicological studies, and establishing a comprehensive quality standard system are current challenges that need to be addressed. In this review, the botany, traditional uses, phytochemistry, pharmacology, and clinical applications of *C. Daphnes*, with the aim of providing a valuable reference for its future development and resource utilization was summarized.

Keywords: *Cortex Daphnes*; botany; phytochemistry; pharmacology; clinical applications; adverse effects and toxicology.

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1. Introduction

China has a rich legacy of herbal medicine, enriched by an abundance of natural medicinal resources. *Cortex Daphnes* belongs to the Thymelaeaceae family and comprises three species: *Daphne giraldii* (Nitsche), *Daphne tangutica* (Maxim), and *Daphne retusa* (Hemsl). The active compounds of *Cortex Daphnes* are found at the root and stem bark. *Cortex Daphnes* was first recorded in the *Shaanxi Materia Medica* [1] and was also included in the *Chinese Pharmacopoeia* (1977 edition) [2]. *C. Daphnes* is warm in nature, with a sour flavor and mild toxicity. It is believed that entering the heart and liver meridians. In clinical treatment, *C. Daphnes* is often utilized in the form of ointments, pills, and injections to treat various pain-related conditions. Although widely distributed throughout China, the wild resources of *C. Daphnes* have sharply declined due to it's long growth cycle, lack of commercialization as a medicinal material, and destructive harvesting practices. Currently, most of the *C. Daphnes* that is available on the market is produced artificially [3].

In 1976, Yu et al. [4] were the first to isolate coumarin compounds from *C. Daphnes* and discovered their remarkable efficacy in pain relief and anti-inflammatory properties. Subsequently, research into the chemical composition of *C. Daphnes* began to intensify. As studies progressed, the discovery of its chemical constituents, along with investigations into its pharmacological activities and mechanisms of action, attracted growing attention from researchers. To date, a total of 284 compounds have been isolated and identified from *C. Daphnes*. The primary chemical constituents are flavonoids and phenylpropanoids [5]. Additionally, *C. Daphnes* contains terpenoids [6], sterols, phenolic acids, alkaloids, organic acids, and other compounds [7]. Modern pharmacological studies have demonstrated that *C. Daphnes* exhibits various pharmacological effects, including anti-inflammatory [8], anti-tumor [9], anti-bacterial [10], immunomodulatory [11], anti-oxidant [12], and analgesic properties [6]. Daphnetin, the primary active constituent of *C. Daphnes*, has been shown to exert anti-inflammatory effects by modulating various pathways [4] and demonstrates significant inhibitory activity against lung cancer [9], breast cancer [13], liver cancer [14], and other malignancies [15]. Clinically, *C. Daphnes* plays a significant role in the treatment of rheumatic pain [16] and is also effective in treating headaches, stomach pain [17], and other types of nerve pain [18].

A review of relevant literature and data from both domestic and international sources over the past four decades reveals that there is currently no systematic review of *C. Daphnes*. Therefore, this paper provides a comprehensive overview of the botany, chemical composition, pharmacological effects, and clinical applications of *C. Daphnes*. This review aims to deepen readers' understanding of *C. Daphnes*, explore its potential biological activities, and provide valuable insights for future research and development in this field.

2. Botany, Description and Distribution

C. Daphnes is commonly used in traditional medicine for dispelling pathogenic wind and alleviating pain in clinical practice. According to scholarly research, *D. odora* was first documented in the *Compendium of Materia Medica* [19], which describes three flower colors: yellow, purple, and white. The yellow variety likely refers to *D. giraldii*, while the purple variety may correspond to *D. tangutica*. The name *C. Daphnes* was first recorded in the *Shaanxi Materia Medica* in 1962 [1].

However, discrepancies exist regarding the botanical origins of *C. Daphnes* across various botanical records and medicinal standards, along with variations in its nomenclature. Based on the information compiled in Table 1, the original plants of *C. Daphnes* are identified as *D. giraldii*, *D. tangutica*, and *D. retusa*.

Table 1. The sources and name of *C. Daphnes* in different flora and medicinal standards

Ancient Book Materials	Source	Name	Ref
Shaanxi Materia Medica	*D. giraldii, D. tangutica, D. retusa*	Zu Shima	[1]
Chinese Pharmacopoeia, 1977	*D. giraldii, D. tangutica, D. retusa*	Zu Shima	[2]
Annals of Medicinal plants in Zhejiang	*D. giraldii*	Zu Shima	[20]
Chinese Materia Medica	*D. giraldii, D. tangutica, D. retusa*	Zu Sima, Zou Sima, Da Jiujia, Huang Yangpi, Pa Yanxiang, Jin Yaodai, Dong Xiaqing, Ai Tuotuo	[21]
The Great Dictionary of Traditional Chinese Medicine	*D. giraldii, D. tangutica, D. retusa*	Zu Sima, Jin Yaodai	[22]
National Compilation of Chinese Herbal Medicine	*D. giraldii*	Zu Shima	[23]
Drug Standards of Gansu, 2020	*D. giraldii, D. tangutica*	Zu Sima, Ma Yaozi, Gou Piliu	[24]
Specification of Processing of Traditional Chinese Medicinal Materials in Henan Province	*D. giraldii, D. tangutica, D. retusa*	Zu Sima, Da Jiujia	[25]
Shanxi Standard of Traditional Chinese Medicinal Materials	*D. giraldii*	Zu Shima	[26]
Specification of Processing of Traditional Chinese Medicinal Materials in Anhui Province	*D. giraldii, D. tangutica*	Zu Shima	[27]
Selection of Chinese Herbal Medicine from Shaanxi-Gansu-Ningxia-Qinghai	*D. giraldii*	Jishi Ruixiang	[28]
Huashan Medical Records	*D. giraldii*	Zou Sima, Da Jiujia	[29]
Annals of Traditional Chinese Medicine in Ningxia	*D. giraldii*	Zu Sima, Ma Yaozi, Ma Doudou	[30]
Annals of Tujia Medicine	*D. retusa*	Jin Yaodai	[31]

According to the records [22], *C. Daphnes* is an erect deciduous shrub that can reach up to 50 cm or taller, with a smooth, hairless stem. The roots are reddish-yellow, and the twigs are green or purplish-brown. The leaves are opposite and often clustered at the tips of the twigs. They are lanceolate, 3-6 cm long, with either pointed or blunt tips, entire margins, wedge-shaped bases, and very short petioles.

Table 2. Similarities and differences between *D. giraldii, D. tangutica,* and *D. retusa*

	D. giraldii	***D. tangutica***	***D. retusa***
Plant height	45-70 cm	50-250 cm	40-150 cm
Branch	Cylindrical, glabrous ; orange yellow; gray brown.	Irregular and multibranched; gray yellow, light gray.	Main stem middle and upper, branches shorter and stiffer.
Leaves	Leaves alternate, 3-6 cm long, 0.7-1.2 cm wide, lateral veins 8-10 pairs, petiole extremely short or absent; celadon.	Leaves alternate, leathery or subleathery, 2-8 cm long, 0.5-1.7 cm wide, petiole short.	Leaves alternate, often clustered on top of twigs, leathery or papery, 1.4-4 cm long, 0.6-1.4 cm wide, petiole very short.
Flowers	Flowers are yellow, slightly aromatic, 3-8 forming terminal heads.	Flowers purple or purplish red outside, capitulum born on tip of twig.	Flowers outside purplish red, inside pink, hairless, aromatic, several flowers form a head.
Ovary	Oval, glabrous, style-free, stigma cephalic.	Oblong obovate, 2-3 mm long, glabrous.	Bottle-shaped or columnar, 2 mm long, glabrous, style extremely short.
Fruit	Ovate or subround, red when mature, 5-6 mm long, 3-4 mm in diameter.	Fruits ovoid or subglobose, glabrous, 6-8 mm long, 6-7 mm in diameter, green, red, purplish black.	Berrylike, ovate or subglobose, 7 mm in diam, green, red.
Flowers period	June	April-May	April-May
Fruiting period	July-August	May-July	June-July
Growing environment	Grows at an altitude of 1600-2600 m at the edge of mountain forest or sparse forest.	Grows in moist forest at an altitude of 1000-3800 m.	grows on alpine grass slopes or under shrubland at an altitude of 3000-3900 m.
Distribution areas	Heilongjiang, Liaoning, Shaanxi, Gansu, Qinghai, Xinjiang and Sichuan.	Shanxi, Shaanxi, Gansu, Qinghai, Sichuan, Guizhou, Yunnan and Tibet.	Shaanxi, Gansu, Qinghai, Hubei, Sichuan, Yunnan and Tibet.

The upper surface is green, while the lower surface is covered with a white, powdery coating. The terminal inflorescence is a head-like cluster consisting of 3-8 flowers, borne on smooth, hairless, short pedicels and lacking bracts. The corolla is yellow, with a tube 6-8 mm long and 4 pointed lobes, each about half the length of the tube. There are 8 stamens in 2 rows, attached near the top of the corolla tube, and the ovary is 1-celled. The berries are oval-shaped and bright red. Flowering occurs in June, with fruiting in July. The medicinal material is characterized by being elongated and curved, with a thickness of 0.5-2 mm. The outer surface of the root bark is reddish-brown and relatively coarse, whereas the outer surface of the stem bark is brownish-yellow or grayish-brown, relatively flat, with longitudinal wrinkles and elongated lenticels.

The cork layer can be easily peeled off in flakes. The interior surface is light yellow to pale brown, featuring longitudinal veins. It is tough, not easily broken, and displays a fibrous appearance at the cross-section. It has a faint odor, a slightly bitter taste, and induces a tingling sensation on the tongue. Preferred characteristics include being long, broad, thick-skinned, and fragrant.

Based on the characteristics documented in the *Flora of China* [32], Table 2 summarizes the differences among the various base plants of *C. Daphnes* in terms of plant height, morphological characteristics, and the distribution of roots, leaves, and flowers. Plant characteristics of *C. Daphnes* are illustrated in Figure 1, while plant distribution is depicted in Figure 2.

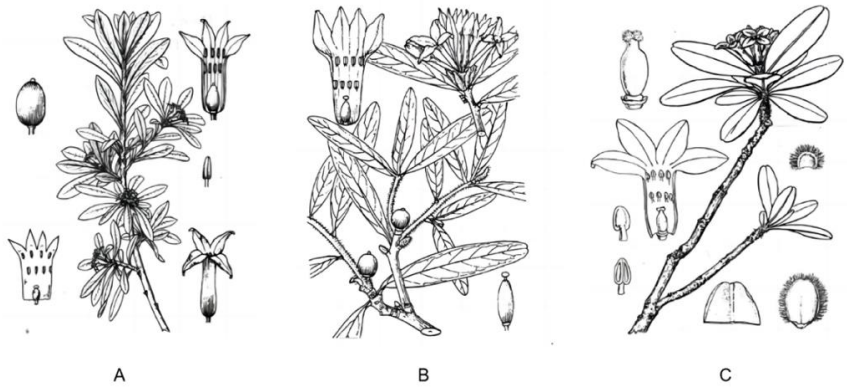

Figure 1. (A): *D. giraldii*; (B): *D. tangutica*; (C): *D. Retusa*

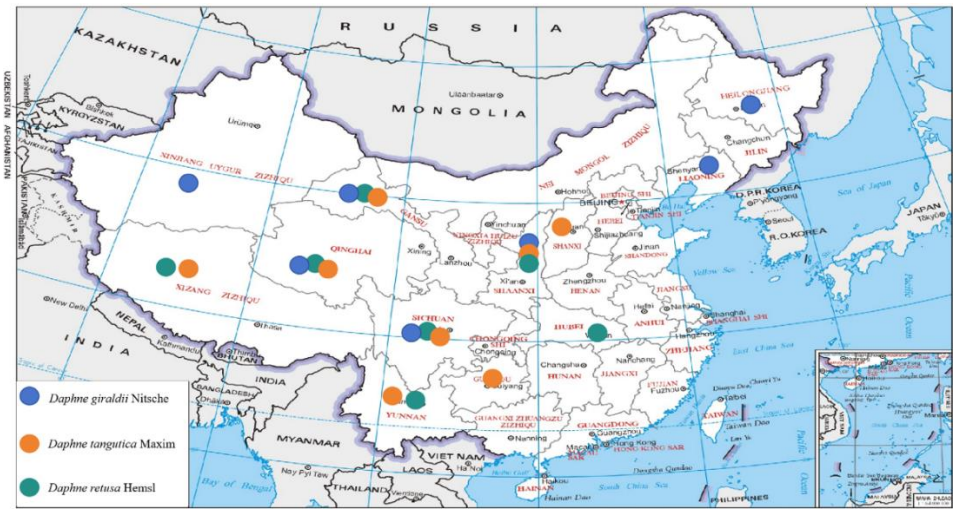

Figure 2. China map of *C. Daphnes* distribution

3. Phytochemistry

To date, researchers have isolated and identified 284 compounds from *C. Daphnes* (Figure 3), with flavonoids (**1**–**104**) and phenylpropanoids (**105**–**191**) as the primary chemical constituents. In addition, it contains terpenoids (**192**–**255**), sterols (**256**–**258**), organic acids (**259**–**267**), phenolics (**268**–**279**), quinones (**280**–**281**), alkaloids (**282**), and other compounds (**283**–**284**). Among these, coumarins (**113**–**163**) are the most widely distributed and were the earliest identified class of major chemically active ingredients in *C. Daphnes*. The names, molecular formulas, sources, and specific structures of compounds in *Cortex Daphnes* are listed in Table 3 and depicted in Figures 4 to 12.

Table 3. Chemical compounds isolated from *C. Daphnes*

No	Compound	Molecular	From	Part	Ref
	Flavonoid compounds				
1	Acacetin	$C_{16}H_{12}O_5$	C	a	[33]
2	Apigenin	$C_{15}H_{10}O_5$	B	a	[34]
3	Apigenin-8-C-glucopyranosy-(1→2)-rhamnopyranoside	$C_{27}H_{31}O_{14}$	B	b	[35]
4	Diosmetin	$C_{16}H_{12}O_6$	C	a	[33]
5	Eupatilin	$C_{18}H_{16}O_7$	A	ab	[36]
6	Genkwanin	$C_{16}H_{12}O_5$	ABC	a	[34, 37, 38]
7	Glucogenkwanin	$C_{22}H_{22}O_{10}$	A	a	[37]
8	Hydroxygenkwanin	$C_{16}H_{12}O_6$	B	b	[35]
9	Luteolin	$C_{15}H_{10}O_6$	AB	a	[34, 39]
10	Luteolin-7-methylether-5-*O*-*β*-D-glucopyranoside	$C_{22}H_{22}O_{11}$	A	a	[37]
11	Luteolin-3′,7-dimethylether-5-*O*-*β*-D-glucopyranoside	$C_{23}H_{24}O_{11}$	A	a	[37]
12	Yuankanin	$C_{27}H_{30}O_{14}$	ABC	ab	[35, 38, 40]
13	6-methoxyflavone	$C_{16}H_{12}O_3$	C	a	[41]
14	7-hydroxyflavone	$C_{15}H_{10}O_3$	C	a	[41]
15	4′,7-dihydroxy-5-methoxyflavone	$C_{16}H_{12}O_5$	A	c	[42]
16	4′,5-dihydroxy-3′,7-dimethoxyflavone	$C_{17}H_{14}O_6$	AC	a	[37]
17	5,7-dihydroxyflavone	$C_{15}H_{12}O_4$	C	a	[41]
18	5,8-dihydroxy-7-methoxy-2-phenyl-4H-1-benzopyran4-one	$C_{16}H_{12}O_5$	C	a	[33]
19	Morusin	$C_{25}H_{24}O_6$	A	ab	[36]
20	Broussoflavonol B	$C_{26}H_{28}O_7$	A	ab	[36]
21	Broussoflavonol F	$C_{25}H_{26}O_6$	A	ab	[43]
22	Daphnegiravone D	$C_{26}H_{28}O_6$	A	ab	[36]
23	Kaempferol	$C_{15}H_{10}O_6$	B	a	[34]
24	Isolicoflavonol	$C_{20}H_{18}O_6$	A	ab	[43]
25	5,7,3′,4′-tetrahydroxy-3-methoxy-8,5′-diprenylflavone	$C_{26}H_{28}O_7$	A	ab	[43]
26	Daphnegiravone A	$C_{26}H_{26}O_7$	A	ab	[36]
27	Daphnegiravone B	$C_{26}H_{26}O_8$	A	ab	[36]
28	Daphneflavan B	$C_{17}H_{16}O_6$	B	b	[44]
29	Daphneflavan C	$C_{24}H_{20}O_8$	B	b	[44]
30	Daphnegiravan M	$C_{16}H_{14}O_4$	A	ab	[45]
31	(2*R*)-kazinol U	$C_{20}H_{22}O_4$	A	ab	[46]
32	(2*S*)-kazinol U	$C_{20}H_{22}O_4$	A	ab	[46]
33	(2*S*)-kazinol I	$C_{25}H_{30}O_4$	A	ab	[45]

34	(2*S*)-7,4′-dihydroxyflavane	$C_{15}H_{14}O_3$	A	ab	[45]
35	(2*S*)-4′-hydroxy-7-methoxyflavan	$C_{16}H_{16}O_3$	A	ab	[45]
36	(2*S*)-7,4′-dihydroxy-3′-prenylflavan	$C_{20}H_{22}O_3$	A	ab	[45]
37	(2*S*)-7,4′-dihydroxy-3′-methoxyflavan	$C_{16}H_{16}O_4$	A	ab	[45]
38	(2*S*)-7,3′-dihydroxy-4′-methoxyflavan	$C_{16}H_{16}O_4$	A	ab	[45]
39	(2*S*)-7-hydroxy-3′,4′-dimethoxyflavan	$C_{17}H_{18}O_4$	A	ab	[45]
40	(2*S*)-7,3′-dimethoxy-4′-hydroxyflavan	$C_{17}H_{18}O_4$	A	ab	[45]
41	Daphnegirin K	$C_{25}H_{30}O_5$	A	ab	[47]
42	Daphnegirin M	$C_{25}H_{30}O_4$	A	ab	[47]
43	Daphnegiralin B1	$C_{25}H_{30}O_5$	A	ab	[48]
44	Daphnegiralin B2	$C_{25}H_{30}O_5$	A	ab	[48]
45	Daphnegiralin B3	$C_{25}H_{30}O_5$	A	ab	[48]
46	Daphnegiralin B4	$C_{25}H_{30}O_5$	A	ab	[48]
47	Daphnegirin L	$C_{25}H_{30}O_4$	A	ab	[47]
48	Daphnegirin T	$C_{25}H_{30}O_5$	A	ab	[47]
49	Daphnegiranol C1	$C_{20}H_{22}O_4$	A	ab	[49]
50	Daphnegiranol C2	$C_{20}H_{22}O_4$	A	ab	[49]
51	Daphnegiranol D1	$C_{25}H_{30}O_4$	A	ab	[49]
52	Daphnegiranol D2	$C_{25}H_{30}O_4$	A	ab	[49]
53	Daphnegiravan E	$C_{25}H_{28}O_5$	A	ab	[45]
54	Daphnegirin C	$C_{25}H_{28}O_5$	A	ab	[47]
55	Daphnegiralin A1	$C_{25}H_{28}O_5$	A	ab	[48]
56	Daphnegiralin A2	$C_{25}H_{28}O_5$	A	ab	[48]
57	Daphnegiralin A3	$C_{25}H_{28}O_5$	A	ab	[48]
58	Daphnegiralin A4	$C_{25}H_{28}O_5$	A	ab	[48]
59	(2*R*)-kazinol B	$C_{25}H_{28}O_4$	A	ab	[46]
60	(2*S*)-kazinol B	$C_{25}H_{28}O_4$	A	ab	[46]
61	Daphnegiravan A	$C_{20}H_{20}O_3$	A	ab	[45]
62	Daphnegiravan B	$C_{21}H_{22}O_4$	A	ab	[45]
63	Daphnegiravan C	$C_{20}H_{20}O_4$	A	ab	[45]
64	Daphnegiravan D	$C_{26}H_{30}O_5$	A	ab	[45]
65	Daphnegiravan L	$C_{25}H_{28}O_4$	A	ab	[45]
66	Daphnegirin N	$C_{20}H_{22}O_4$	A	ab	[47]
67	Daphnegirin R	$C_{25}H_{30}O_4$	A	ab	[47]
68	Daphnegiravan G	$C_{25}H_{30}O_4$	A	ab	[45]
69	Daphnegirin Q	$C_{25}H_{28}O_4$	A	ab	[47]
70	Daphnegirin G	$C_{25}H_{30}O_4$	A	ab	[47]
71	Daphnegiralin C1	$C_{20}H_{22}O_4$	A	ab	[48]
72	Daphnegiralin C2	$C_{20}H_{22}O_4$	A	ab	[48]
73	Daphnegiralin D1	$C_{25}H_{30}O_5$	A	ab	[48]
74	Daphnegiralin D2	$C_{25}H_{30}O_5$	A	ab	[48]
75	(2*R*)-daphnegiranol A	$C_{20}H_{20}O_4$	A	ab	[46]
76	(2*S*)-daphnegiranol A	$C_{20}H_{20}O_4$	A	ab	[46]
77	(2*R*)-daphnegiranol B	$C_{20}H_{22}O_4$	A	ab	[46]
78	(2*S*)-daphnegiranol B	$C_{20}H_{22}O_4$	A	ab	[46]
79	Daphnegiravan F	$C_{22}H_{22}O_4$	A	ab	[45]
80	Daphnegiravan I	$C_{25}H_{26}O_4$	A	ab	[45]
81	Daphnegiravan J	$C_{25}H_{28}O_4$	A	ab	[45]
82	Daphnegiravan K	$C_{22}H_{20}O_4$	A	ab	[45]
83	Daphnegiralin K	$C_{25}H_{28}O_5$	A	ab	[47]
84	Afzelechin-5-*O*-methyl	$C_{16}H_{16}O_5$	A	ac	[50]
85	Afzelechin-7-*O*-*β*-glucopyranoside	$C_{21}H_{24}O_{10}$	A	a	[37]
86	Afzelechin-5-*O*-methyl-7-*O*-*β*-glucopyranoside	$C_{22}H_{26}O_{10}$	A	a	[37]
87	Afzelechin5-p-hydroxybezoxy-7-hydroxyl-8-etho-xycarbonyl	$C_{25}H_{22}O_9$	A	a	[37]

88	Afzelechin-5-p-hydroxybezoxy-7-(3,4,6-trihydroxybezoxy)-8-ethoxy-carbonyl	$C_{32}H_{26}O_{13}$	A	a	[37]
89	Afzelechin-5-p-hydroxybezoxy-7-(3,4,6-trihydroxybezoxy)-8-methoxy-carbonyl	$C_{31}H_{24}O_{13}$	A	a	[37]
90	Sakuranin	$C_{22}H_{24}O_{10}$	AB	a	[6, 37]
91	(2*S*)-sakuranetin	$C_{16}H_{14}O_5$	B	a	[6]
92	Daphnegiravone C	$C_{26}H_{28}O_7$	A	ab	[36]
93	Daphnodorin A	$C_{30}H_{22}O_9$	AC	ab	[38, 39, 51]
94	Daphnodorin B	$C_{30}H_{22}O_{10}$	AC	ab	[38, 39, 51]
95	Daphnodorin C	$C_{30}H_{22}O_9$	AC	ab	[38, 39, 51]
96	Genkwanin A	$C_{30}H_{22}O_{10}$	C	a	[33]
97	Daphnodorin E	$C_{30}H_{22}O_{10}$	C	a	[38]
98	Daphnodorin F	$C_{30}H_{22}O_{10}$	C	a	[38]
99	Daphnodorin J	$C_{30}H_{24}O_9$	C	a	[33]
100	Dihydrodaphnodorin B	$C_{30}H_{24}O_{10}$	C	a	[33]
101	Daphnodorin D1	$C_{30}H_{22}O_9$	AB	ab	[44, 52]
102	Daphnodorin D2	$C_{30}H_{20}O_9$	B	b	[44]
103	Daphnogirin A	$C_{30}H_{22}O_{10}$	A	ab	[53]
104	Daphnogirin B	$C_{30}H_{22}O_{10}$	A	ab	[53]
	Phenylpropanoid compounds				
105	Caffeic acid n-dueicosanyl estre	$C_{29}H_{48}O_4$	B	b	[35]
106	Docosyl(2*E*)-3-(3,4-dihydroxyphenyl) acrylate	$C_{31}H_{52}O_4$	B	b	[35]
107	(*Z*) Octadecyl caffeate	$C_{27}H_{44}O_4$	AC	a	[33, 54]
108	Sinapaldehyde glucopyranoside	$C_{17}H_{22}O_9$	A	a	[37]
109	Sinapyl alcohol-1,3′-diglucopyranoside	$C_{23}H_{34}O_{16}$	A	ab	[37, 55]
110	Daphnenone	$C_{17}H_{16}O_2$	B	ab	[35, 6]
111	Syringin	$C_{17}H_{24}O_9$	ABC	ab	[35, 37, 38]
112	n-butyl syringin	$C_{21}H_{27}O_9$	A	a	[39]
113	Cichoriin	$C_{15}H_{16}O_9$	C	bc	[56]
114	Daphnetin	$C_9H_6O_4$	ABC	abc	[34, 35, 37, 56]
115	Daphnoside	$C_{15}H_{16}O_9$	ABC	abc	[34, 35, 37, 56]
116	Daphnetin-8-*O*-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside	$C_{21}H_{26}O_{14}$	A	a	[34, 35, 37, 56]
117	Daphnin	$C_{15}H_{16}O_9$	AB	ab	[4, 34, 35, 37]
118	Daphneside	$C_{21}H_{26}O_{14}$	A	a	[40]
119	7,8-dimethoxycoumarin	$C_{11}H_{10}O_4$	A	a	[58]
120	7-hydroxy-8-methoxycoumarin	$C_{10}H_8O_4$	ABC	a	[34, 38]
121	8-hydroxy-7-methoxycoumarin	$C_{10}H_8O_4$	ABC	a	[34, 38]
122	Umbelliferone	$C_9H_6O_3$	ABC	ab	[33,35, 37]
123	Umbeliferone-7-*O*-*β*-D-glucopyranoside	$C_{15}H_{16}O_8$	ABC	a	[34, 38]
124	4-methyl-7-hydroxycoumarin	$C_{10}H_8O_3$	A	a	[58]
125	5-hydroxy-7-methoxycoumarin-8-*O*-*β*-D-glucopyranoside	$C_{16}H_{18}O_9$	A	a	[58]
126	Daphnegiratin A	$C_{14}H_{14}O_4$	A	ab	[43]
127	Daphnegiratin B	$C_{19}H_{22}O_4$	A	ab	[43]
128	Osthole	$C_{15}H_{16}O_3$	B	b	[7]
129	7-demethylsuberosin	$C_{14}H_{14}O_3$	A	ab	[43]
130	5,7-dihydroxy-6,8-di-(3,3-dimethylallyl)-coumarin	$C_{19}H_{22}O_4$	A	ab	[43]
131	Aphegiractin A1	$C_{14}H_{14}O_5$	A	ab	[59]
132	Aphegiractin A2	$C_{14}H_{14}O_5$	A	ab	[59]
133	Luvangetin	$C_{15}H_{14}O_4$	A	a	[43]

134	8-hydroxyxanthyletin	$C_{14}H_{12}O_4$	A	ab	[43]
135	Daphneticin	$C_{20}H_{18}O_8$	AB	ac	[50, 60]
136	Daphneticin-4′′-*O*-*β*-D-glucopyranoside	$C_{26}H_{28}O_{13}$	C	d	[61]
137	Isodaphneticin	$C_{19}H_{16}O_7$	AC	abc	[50, 56]
138	Nodakenetin	$C_{14}H_{14}O_4$	A	ab	[47]
139	8-Methoxymarmesin	$C_{15}H_{16}O_5$	A	ab	[47]
140	Bicoumastechamin	$C_{19}H_{12}O_6$	A	a	[39]
141	Daphjamilin	$C_{24}H_{20}O_{10}$	AC	ad	[61, 62]
142	7,7′-dihydroxy-[6,8′-bi-2H-benzopyran]-2,2′-dione	$C_{18}H_{10}O_6$	A	a	[63]
143	Edgeworside C	$C_{24}H_{20}O_{10}$	AC	a	[38, 64]
144	Giraldoid A	$C_{24}H_{20}O_{11}$	AB	a	[34, 65]
145	Daphnogirin	$C_{19}H_{12}O_6$	A	ac	[50]
146	Daphnogirin-6-*O*-*β*-D-apiofuranosyl	$C_{24}H_{20}O_{11}$	A	a	[37]
147	Daphnogirin-6-*O*-*α*-L-rhamnnopyranosyl	$C_{25}H_{12}O_{11}$	A	a	[37]
148	Daphnolin	$C_{24}H_{20}O_{13}$	A	a	[63]
149	Daphgilin	$C_{18}H_{10}O_8$	A	a	[62]
150	Daphneretusin A	$C_{24}H_{20}O_{12}$	C	d	[61]
151	Daphnoretin	$C_{19}H_{12}O_7$	ABC	abc	[34, 56, 66]
152	Daphnorin	$C_{25}H_{22}O_{12}$	AB	ab	[35, 63]
153	Edgeworin	$C_{18}H_{10}O_6$	A	ab	[67]
154	Edgeworthin	$C_{18}H_{10}O_7$	A	ab	[68]
155	Rutarensin	$C_{31}H_{30}O_{16}$	A	a	[62]
156	Rutamontine	$C_{19}H_{12}O_7$	C	a	[33]
157	Daphnogitin	$C_{18}H_{10}O_6$	A	ac	[50]
158	Lasiocephalin	$C_{19}H_{12}O_6$	A	ac	[50, 69]
159	Isodaphnorin	$C_{19}H_{12}O_7$	C	bc	[56]
160	Daphneretusin B	$C_{33}H_{24}O_{15}$	C	d	[61]
161	Edgeworside A	$C_{33}H_{24}O_{13}$	C	a	[38]
162	Neodaphnoretin	$C_{33}H_{24}O_{14}$	AC	a	[33]
163	8-[10]-7-hydroxy-3-[(2-oxo-2H-1-benzopyran-7-yl) oxy]-2H-1-benzopyran-2-one	$C_{33}H_{25}O_{13}$	C	d	[61]
164	Secoisolariciresinol-9,9′-acetonide	$C_{23}H_{30}O_6$	B	a	[6]
165	Secroisolariciresinol	$C_{20}H_{26}O_6$	AB	a	[6, 37]
166	Acuminatin	$C_{20}H_{24}O_6$	AB	ac	[6, 50]
167	(−)-Dihydrosesamin	$C_{20}H_{20}O_6$	AB	abc	[50, 70]
168	(−)-Lariciresinol	$C_{20}H_{24}O_6$	AB	a	[7, 37]
169	(−)-Lariciresinol-4-*O*-*β*-D-glucopyranoside	$C_{26}H_{34}O_{11}$	A	a	[37]
170	Isocubebin	$C_{20}H_{20}O_6$	BC	a	[6,33]
171	4,4′-dihydroxy-3,3′-dimethoxy-9-ethoxy-9,9′-epoxylignan	$C_{22}H_{28}O_6$	B	a	[6]
172	(8*S*,9*S*,8′*S*)-4,4′-dihydroxy-3,3′,9-trimetoxy-9,9′-epoxylignan	$C_{21}H_{24}O_7$	B	a	[6]
173	(8*S*,9*R*,8′*S*)-4,4′-dihydroxy-3,3′,9-trimetoxy-9,9′-epoxylignan	$C_{21}H_{24}O_7$	B	a	[6]
174	Daphnetone	$C_{22}H_{26}O_7$	B	a	[6]
175	Matairesinol	$C_{20}H_{22}O_6$	AB	a	[6, 71]
176	(+)-Nortrachelogenin	$C_{20}H_{22}O_7$	AB	ab	[6, 66]
177	Pluviatolide	$C_{20}H_{20}O_6$	B	a	[6]
178	Isosalicifoline	$C_{20}H_{20}O_6$	A	ac	[50]
179	Daphnretusic acid	$C_{19}H_{20}O_8$	C	d	[41]
180	Woonenenoside XI	$C_{26}H_{30}O_{11}$	A	ab	[72]
181	(7′S,8′R,8R)-isolariciresinol	$C_{20}H_{24}O_6$	B	a	[6]
182	(−)-Pinoresinol	$C_{20}H_{22}O_6$	ABC	abc	[38, 50, 70]
183	(−)-Pinoresinol-4-*O*-*β*-D-glucopyranoside	$C_{26}H_{32}O_{11}$	A	a	[37]
184	(−)-Pinoresinol-4,4′-di-*O*-*β*-D-glucopyranoside	$C_{32}H_{42}O_{16}$	A	a	[37]

185	(+)-Syringaresinol	$C_{22}H_{26}O_8$	AB	ab	[37, 70]
186	Eleutheroside E	$C_{34}H_{46}O_{18}$	A	a	[37]
187	(+)-Liriorosinol-B-dimethylether	$C_{24}H_{30}O_8$	A	a	[71]
188	(+)-Medioresinol	$C_{21}H_{24}O_7$	B	b	[7]
189	(+) Sesamin	$C_{20}H_{18}O_6$	C	d	[41]
190	Piperitol	$C_{20}H_{20}O_6$	BC	ab	[6, 33]
191	3,3′-bis (3,4-dihydro-4-hydroxy-6 methoxy-2H-1-benzopyran)	$C_{20}H_{22}O_6$	B	a	[6]
	Terpenoid compounds				
192	Byzantionoside B	$C_{19}H_{32}O_7$	B	d	[73]
193	Auranticanol A	$C_{15}H_{20}O_3$	B	d	[73]
194	Chamaejasmone D	$C_{15}H_{22}O_3$	B	d	[73]
195	Selleraterpenoid B	$C_{16}H_{22}O_4$	B	d	[73]
196	Daphnoid A	$C_{15}H_{18}O_4$	B	a	[37]
197	Daphnauranol B	$C_{16}H_{20}O_2$	B	d	[73]
198	Daphnauranol D	$C_{16}H_{22}O_4$	B	d	[73]
199	Tanguticatin L	$C_{15}H_{20}O_2$	B	d	[73]
200	Daphneguaine B	$C_{15}H_{22}O_3$	B	d	[73]
201	Daphneguaine G	$C_{15}H_{22}O_3$	B	d	[73]
202	Wikstronone A	$C_{15}H_{22}O_2$	B	d	[73]
203	1*α*,7*α*,10*α*-guaia-4,11-dien-3one	$C_{15}H_{22}O$	C	a	[33]
204	1*β*-hydroxy-10*β*H-guai-4,11-dien-3-one	$C_{15}H_{22}O_2$	B	d	[73]
205	Daphneaine F	$C_{15}H_{20}O_2$	B	d	[73]
206	(+)-13-hydroxy-1*α*H,7*α*H,10*α*H-guaia-4,11-dien-3-one	$C_{15}H_{20}O_3$	B	d	[73]
207	Tanguticatin J	$C_{16}H_{24}O_3$	B	d	[73]
208	Tanguticatin I	$C_{15}H_{22}O_2$	B	d	[73]
209	(1*S*,7*R*,10*S*,11*R*)-3-oxoguai-4-ene-11,12-diol	$C_{15}H_{24}O_3$	B	d	[73]
210	(1*S*,7*R*,10*S*,11*S*)-3-oxoguai-4-ene-11,12-diol	$C_{15}H_{24}O_3$	B	d	[73]
211	Oleodaphnal	$C_{15}H_{18}O_2$	A	a	[37]
212	Oleodaphnone	$C_{15}H_{18}O_2$	C	a	[33]
213	Tanguticatin K	$C_{15}H_{20}O_2$	B	d	[73]
214	Tanguticatin G	$C_{16}H_{20}O_4$	B	d	[73]
215	Tanguticatin H	$C_{16}H_{20}O_4$	B	d	[73]
216	Anhydrogeigerin	$C_{15}H_{18}O_3$	B	a	[6]
217	Daphnoid B	$C_{18}H_{26}O_5$	B	ad	[6, 73]
218	Tanguticatin E	$C_{16}H_{24}O_3$	B	d	[73]
219	Tanguticatin F	$C_{15}H_{20}O_3$	B	d	[73]
220	Tanguticatin A	$C_{15}H_{20}O_4$	B	d	[73]
221	Tanguticatin B	$C_{15}H_{22}O_2$	B	d	[73]
222	Tanguticatin C	$C_{15}H_{23}O_2$	B	d	[73]
223	Tanguticatin D	$C_{15}H_{23}O_2$	B	d	[73]
224	Daphnegiraldigin	$C_{27}H_{32}O_9$	AB	ad	[37, 74]
225	Prostratin	$C_{22}H_{30}O_6$	B	d	[73]
226	5*β*–OH–prostratin	$C_{22}H_{30}O_7$	B	d	[73]
227	Excoecafolin A	$C_{23}H_{32}O_7$	B	d	[73]
228	Hlosericin B	$C_{15}H_{22}O_3$	B	d	[73]
229	12-hydroxy-4,5-epoxy-caryophyllene	$C_{15}H_{24}O_2$	B	d	[73]
230	Acutilobin E	$C_{37}H_{38}O_{12}$	C	a	[33]
231	Daphnetoxin	$C_{27}H_{30}O_8$	AB	a	[6, 54]
232	Daphnegiraldicin	$C_{34}H_{40}O_{10}$	A	a	[75]
233	Daphnegiraldidin	$C_{39}H_{52}O_{10}$	A	a	[76]
234	Daphnegiraldifin	$C_{43}H_{60}O_9$	A	ab	[77]
235	Excoecariatoxin	$C_{30}H_{40}O_8$	B	ad	[6, 34]

236	Altadaphnan C	$C_{37}H_{42}O_{10}$	B	d	[74]
237	Gniditrin	$C_{37}H_{42}O_{10}$	ABC	ad	[6, 33, 54, 74]
238	Gnidicin	$C_{36}H_{36}O_{10}$	ABC	ad	[33, 54, 74]
239	Tanguticanine A	$C_{35}H_{40}O_{10}$	B	d	[74]
240	Tanguticanine C	$C_{35}H_{40}O_{12}$	B	d	[74]
241	Tanguticanine D	$C_{37}H_{44}O_{12}$	B	d	[74]
242	Tanguticanine E	$C_{38}H_{46}O_{12}$	B	d	[74]
243	Tanguticanine F	$C_{39}H_{46}O_{10}$	B	d	[74]
244	Hirsein A	$C_{37}H_{44}O_{10}$	B	d	[74]
245	Yuanhuacin	$C_{37}H_{44}O_{10}$	B	a	[6]
246	Yuanhuajine	$C_{37}H_{42}O_{10}$	B	a	[6]
247	Simplexin	$C_{30}H_{44}O_8$	B	d	[74]
248	12-hydroxydaphnetoxin	$C_{27}H_{30}O_9$	AB	abd	[74, 77]
249	9,13,14-ortho-(2,4,6-decatrienoate) of 5*β*-hydroxyresiniferonol-6*α*,7*α*-oxide	$C_{30}H_{38}O_8$	B	a	[6]
250	Tanguticanine B	$C_{37}H_{44}O_{11}$	B	d	[74]
251	Tanguticatin M	$C_{30}H_{46}O_3$	B	d	[73]
252	*β*-Amyrone	$C_{30}H_{48}O$	A	a	[39]
253	*β*-Amyrin acetate	$C_{32}H_{52}O_2$	A	a	[39]
254	Oleanic acid	$C_{30}H_{48}O_3$	A	a	[37]
255	Betulinic acid	$C_{30}H_{48}O_3$	A	a	[55]
	Other compounds				
256	Daucosterol	$C_{35}H_{60}O_6$	C	a	[41]
257	*β*-sitosterol	$C_{29}H_{50}O$	AB	ab	[37, 78]
258	*β*-sitosteryl palmitate	$C_{45}H_{80}O_2$	AB	ad	[39, 69]
259	Benzoic acid	$C_7H_6O_2$	B	d	[7]
260	Glycerol monostearol acid	$C_{21}H_{46}O_4$	A	a	[54]
261	Glyceryl tristearate	$C_{57}H_{110}O_6$	B	b	[70]
262	Phytol	$C_{20}H_{40}O$	B	d	[7]
263	Lauric acid	$C_{12}H_{24}O_2$	B	ab	[78]
264	n-octacosanoic acid	$C_{28}H_{56}O_2$	B	b	[35]
265	n-tetrateiacontanol	$C_{34}H_{70}O$	B	b	[35]
266	Nonacosane	$C_{29}H_{60}$	A	c	[42]
267	Palmitic acid	$C_{16}H_{32}O_2$	B	ab	[78]
268	Broussonin A	$C_{16}H_{18}O_3$	A	ab	[79]
269	Broussonin B	$C_{16}H_{18}O_3$	A	ab	[79]
270	Broussonin E	$C_{17}H_{20}O_4$	A	ab	[79]
271	Daphnegiranin A	$C_{21}H_{26}O_3$	A	ab	[79]
272	Syringaldehyde	$C_9H_{10}O_4$	BC	ab	[6, 35, 38]
273	p-hydroxybenzoic acid	$C_7H_6O_3$	AB	ab	[37, 78]
274	Daphneolone	$C_{17}H_{18}O_3$	ABC	ab	[6, 35, 38, 80]
275	Daphnolon	$C_{17}H_{18}O_2$	AB	a	[6, 63]
276	threo-1,5-diphenylpentane-1,3-diol	$C_{17}H_{20}O_2$	B	a	[6]
277	*S*-(+)-1-(4-methoxyphenyl)-3-hydroxy-5-phenyl-1-pentanone	$C_{18}H_{20}O_3$	A	ab	[79]
278	*R*-(−)-1-(4′-hydroxyphenyl)-3-hydroxy-5-phenyl-1,5-pentandione	$C_{17}H_{16}O_4$	A	ab	[79]
279	*S*-(+)-1-(4-hydroxy-3-methoxyphenyl)-3-hydroxy-5-phenyl-1-pentanone	$C_{18}H_{20}O_4$	B	a	[6]
280	Physcion	$C_{16}H_{32}O_5$	B	bd	[35, 70]
281	*α*-Tocophexolquinone	$C_{29}H_{50}O_3$	C	a	[33]
282	Aurantiamide acetate	$C_{27}H_{28}N_2O_4$	B	a	[6]
283	Butyl Isobutyl Phthalate	$C_{16}H_{22}O_4$	C	a	[33]

284	Ethyl-*O*-*β*-D-glucopyranoside	$C_8H_{16}O_6$	A	a	[37]

Notes: A (*D. giraldii***); B (***D. tangutica***); C (***D. retusa***); a (**stem bark**); b (**root bark**); c (**leaf**); d (**whole herb**)**

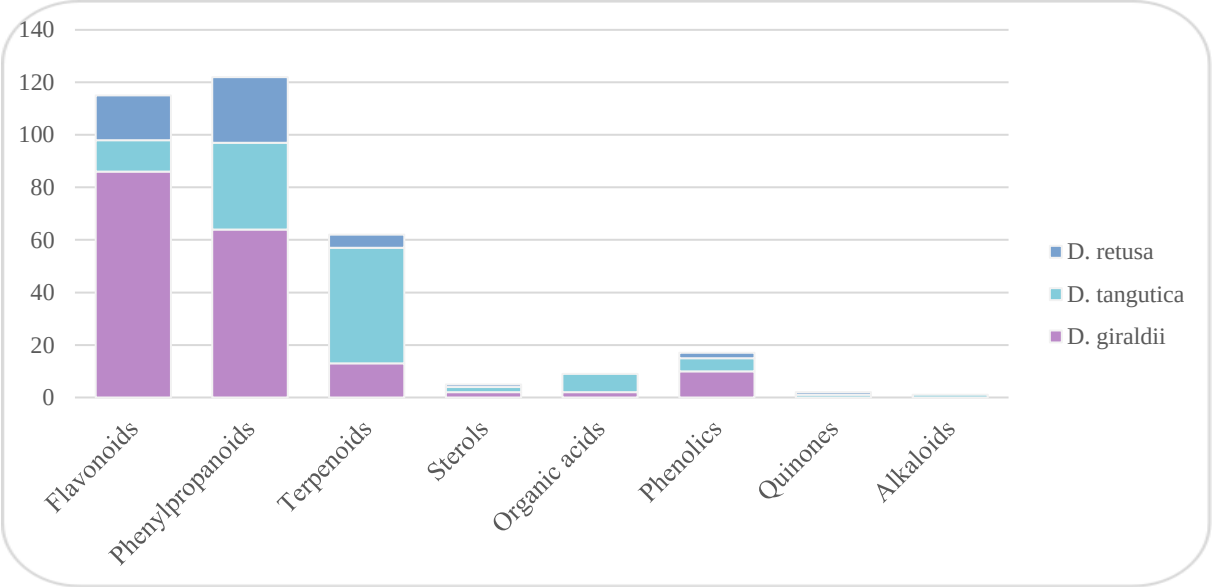

Figure 3. The types and number of compounds fractionated in *C. Daphnes*

3.1. Flavonoids and Flavan Compounds

The primary constituents of *C. Daphnes* include flavones, flavonols, flavans, bisflavonoids, flavanols, and flavanones. Flavonoids (**1–19**) are characterized by a fundamental 2-phenylchromen nucleus, featuring a C_6-C_3-C_6 backbone structure, with no oxygen-substituted groups at the C-3 position and hydroxyl (OH) or methoxy (OCH_3) substituents typically at the C-5 and C-7 positions. Flavonols (**20–27**) are distinguished by the presence of a hydroxyl group (-OH) at the C-3 position of the flavone nucleus. Flavans (**28–83**) predominate in *C. Daphnes*, serving as the foundational structure for flavonoids. In this structure, the double bond at positions C_2-C_3 of the flavone structure is hydrogenated, and there are no substituents at positions C-3 and C-4. Six flavanols (**84–89**) of the flavan-3-ol type have been isolated from *C. Daphnes*. Su first isolated a flavanone glycoside compound, Sakuranin (**90**), from the stem bark of *D. giraldii* [37]. Biflavonoids (**93–104**) are dimers formed by linking two flavonoid derivatives through C–C or C–O–C bonds. These compounds exhibit significant biological activities, including notable antioxidant effects demonstrated by Daphnogirin A (**103**) and Daphnogirin B (104) [53].

Moreover, studies have shown that most flavonoid compounds bind to sugars, resulting in their existence as glycosides within plants. However, from *C. Daphnes*, a total of **104** compounds have been isolated and identified, of which only eight contain sugar substituents. Additionally, **39** flavonoid compounds contain an isoprenyl group, which enhances lipid solubility and strengthens the ability of cell membranes to interact with various cellular targets. For example, in inducing apoptosis in Hep3B cells, Daphnegiranol D1 (51) exhibited greater potency than Daphnegiranol C1 (**49**) [49]. Figures 4 to 6 display the specific structures of these compounds.

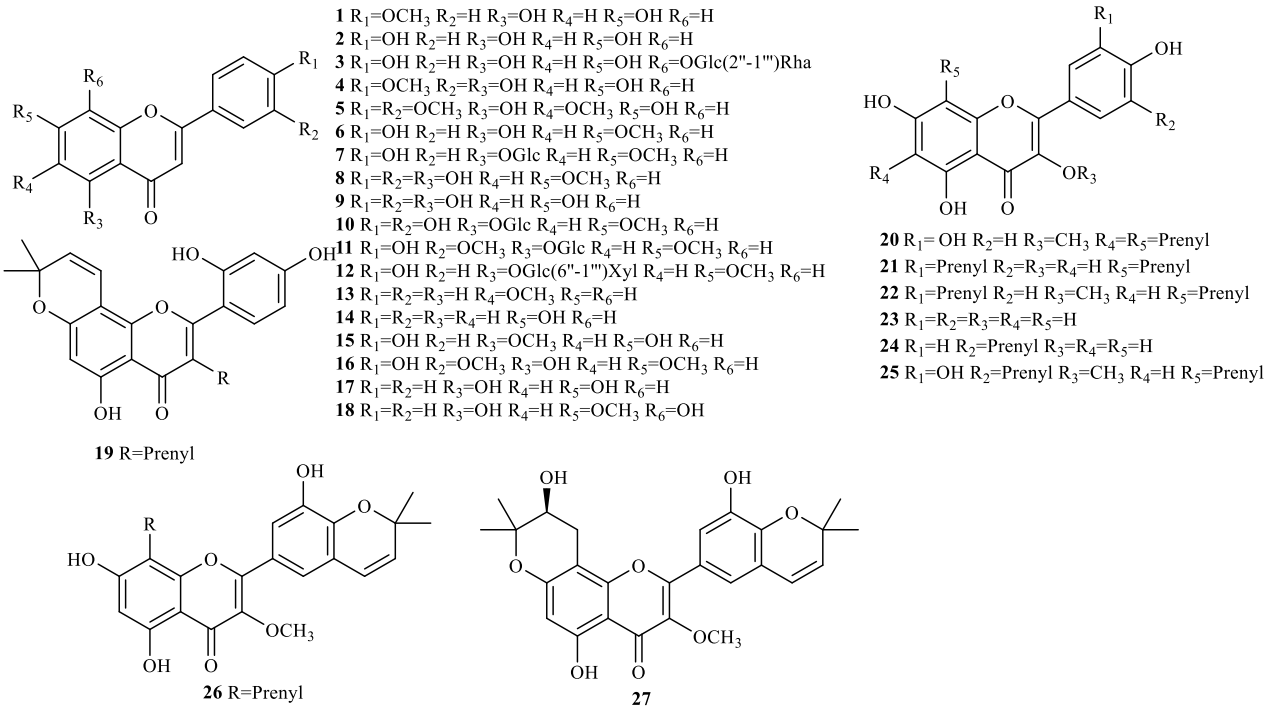

Figure 4. The structures of flavones and flavonols (**1**-**27**) isolated from *C. Daphnes*

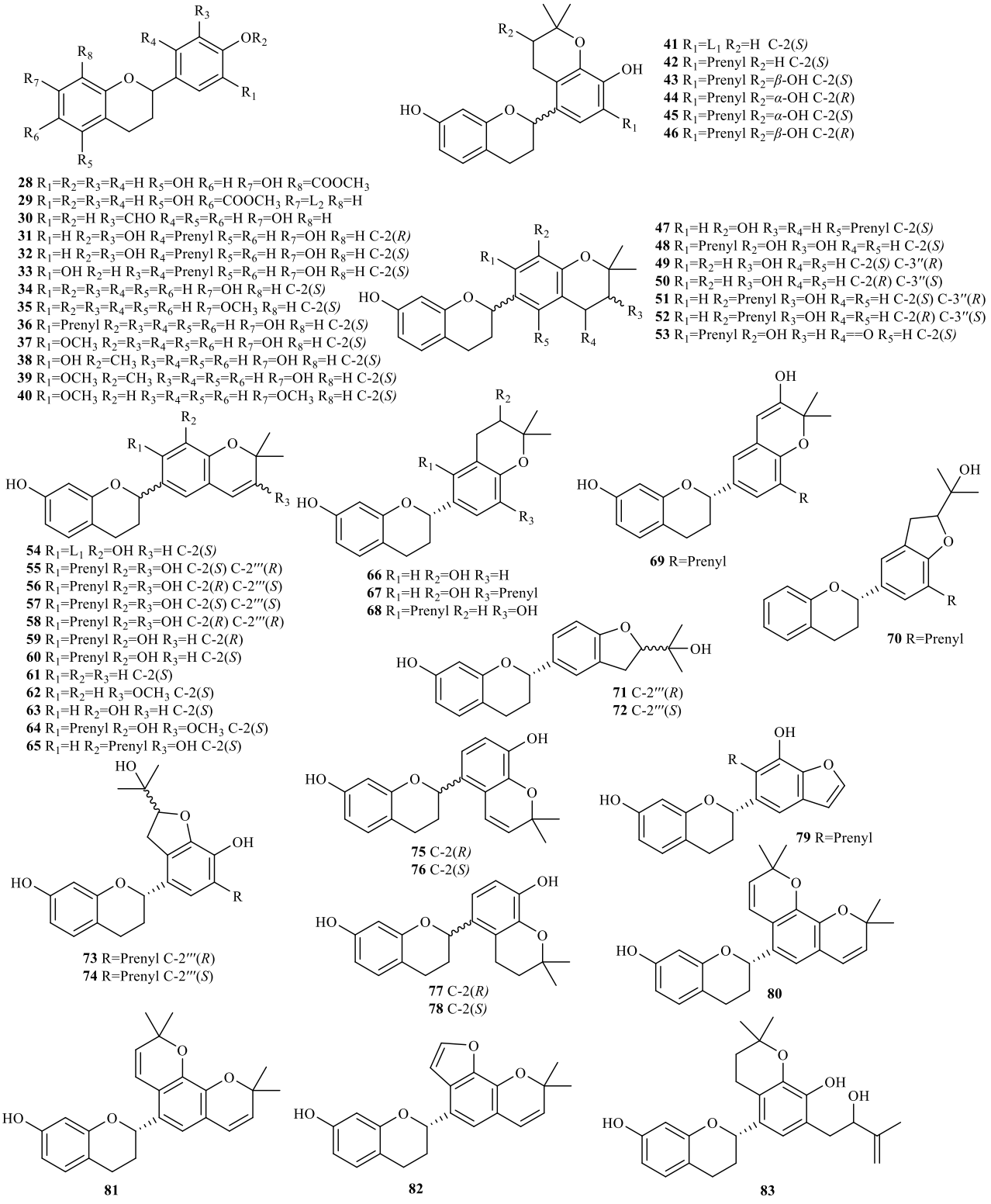

Figure 5. The structures of flavans (**28-83**) isolated from *C. Daphnes*

3.2. Phenylpropanoids Compounds

3.2.1. Simple Phenylpropanoids

Eight simple phenylpropanoid compounds (**105-112**) have been isolated from *C. Daphnes*. These compounds are benzylpropane derivatives characterized by a C_6-C_3 backbone. They can be classified into phenylpropanes, phenylpropanols, phenylpropanals, phenylpropanoic acids, and their derivatives, based on the different substituents attached to the C-3 side chain. In *C. Daphnes*, phenylpropanoic acid and its derivatives predominantly exist within the plant. Zhang [35] firstly isolated a novel natural product, daphnenone (**110**) from *D. tangutica*. Additionally, one phenylpropanal (**108**) and two phenylpropanol compounds (**111-112**) were also obtained. The detailed structures of these compounds are illustrated in Figure 7.

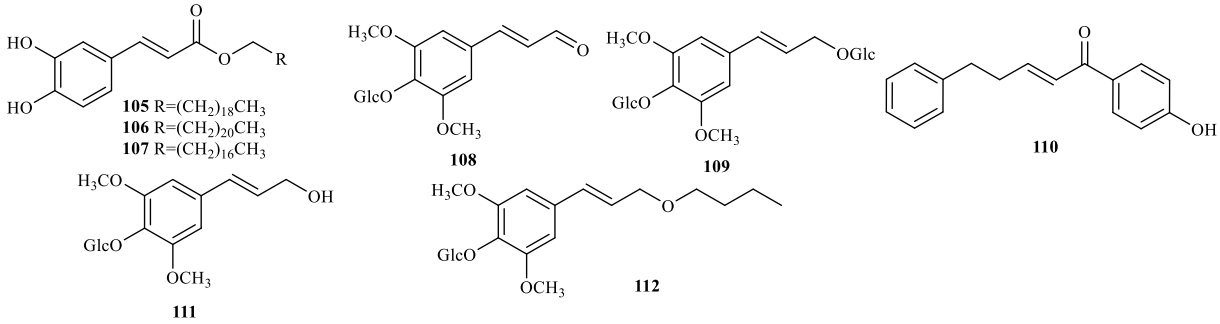

Figure 7. The structures of simple phenylpropanoids (**105-112**) isolated from *C. Daphnes*

3.2.2. Coumarins Compounds

Coumarins are the primary pharmacologically active compounds within *C. Daphnes*. These compounds are characterized by a lactone structure featuring a benzopyran-*α*-pyrone nucleus. To date, **51** coumarin compounds (**113–163**) have been isolated from *C. Daphnes*, all of which exhibit substitution at the C-7 position. Coumarins are classified into simple coumarins, furanocoumarins, pyranocoumarins, and other types. This classification is based on the presence or absence of substitutions on the *α*-pyrone ring and the formation of additional rings through C-6 and C-8.

Simple coumarins (**113–130**) are characterized by substituents such as hydroxyl (OH), methoxy (OCH_3), sugar groups, or isopentenyl derivatives located exclusively on one side of the benzene ring, with no condensation between the C-7 and C-6(8) positions to form a cyclic substituent. Two monomeric compounds, daphnetin (**114**) and daphnin (**117**), have been isolated from *C. Daphnes* [4]. Daphnetin is abundantly present in *C. Daphnes*. It is not only an active ingredient in the plant but also a newly developed drug pioneered in China [81]. Su et al. [57] isolated a disaccharide glucoside, compound **116**, from the stem bark of *D. giraldii*. Pyranocoumarins (**131–137**) are derived from simple coumarins, where the C-6 (or C-8) position is alkylated to form an isopentenyl group, which then condenses with the hydroxyl group at C-7 to form a pyran ring. If C-6 condenses with C-7, the result is a linear pyranocoumarin, whereas if C-8 condenses with C-7, it forms an angular pyranocoumarin. Zhang et al. [59] isolated two new compounds, aphegiractin A1 and A2 (**131–132**), from the stem bark of *D. giraldii*. These compounds exhibited significant antioxidant activity and tyrosinase inhibition.

Furanocoumarins share a structural similarity with pyranocoumarins. In furanocoumarins, the hydroxyl group at the C-7 position condenses with C-6 (or C-8) to form a five-membered furan ring.

Li [47] firstly isolated and identified two linear furanocoumarins, nodakenetin (**138**) and 8-methoxymarmesin (**139**), from the stem bark of *D. giraldii*.

Additionally, certain derivatives, known as bis-coumarins (**140-163**), are formed by linking two or three coumarin units through C-C or C-O bonds. Hu et al. [38] were the first to isolate edgeworside A (**161**) and edgeworside C (**142**) from *D. retusa*. Su [37] isolated daphnoretin (**151**) from *D. giraldii*. The detailed structures of these compounds are illustrated in Figure 8.

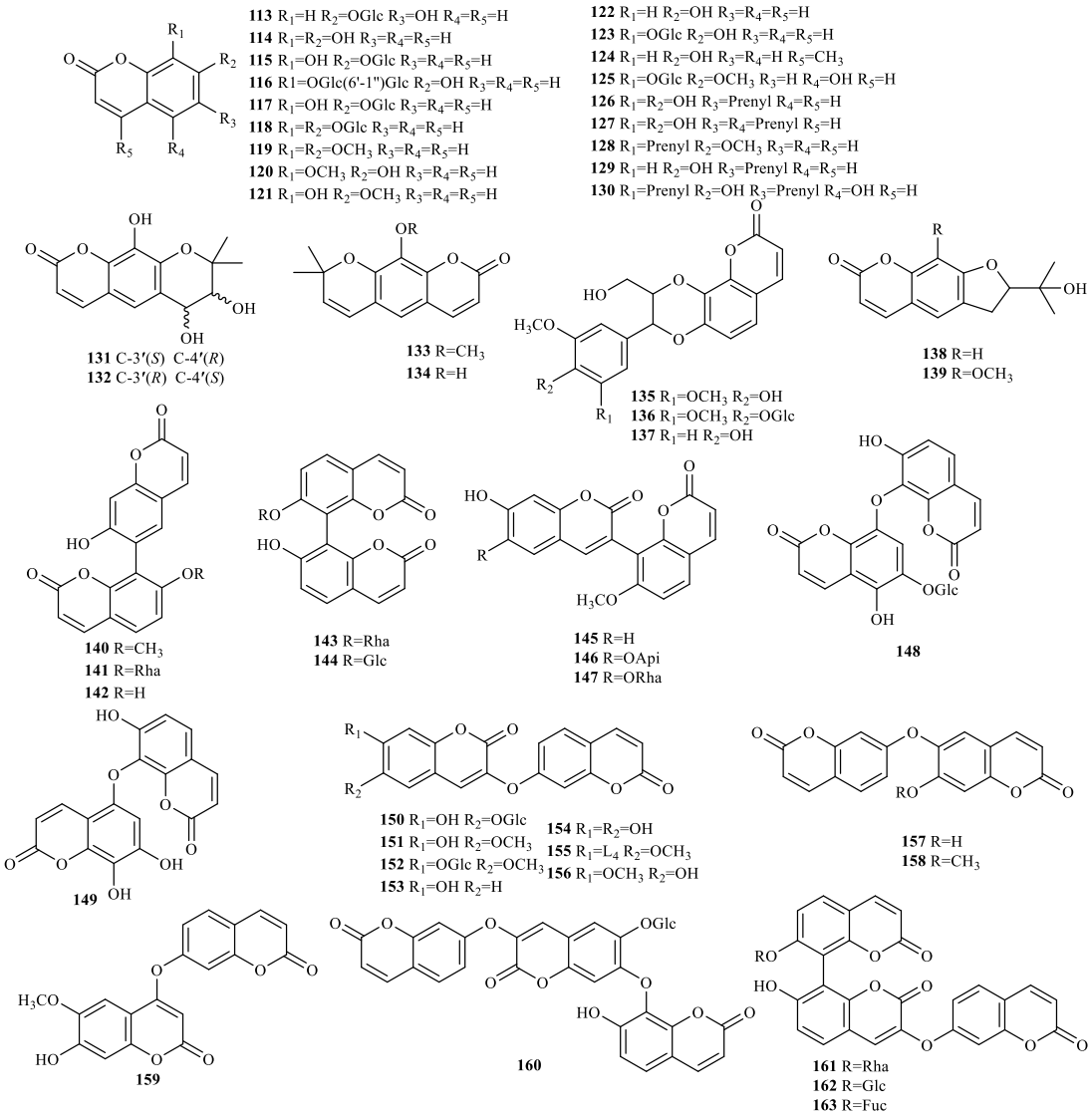

Figure 8. The structures of coumarins (**113-163**) isolated from *C. Daphnes*

3.2.3. Lignans Compounds

Lignans (**164-188**) are compounds that result from the polymerization of two or more phenylpropanoid derivatives. To date, 27 lignan compounds have been isolated from *C. Daphnes*. These compounds are structurally classified into simple lignans (**164-165**), monoepoxylignans (**166-173**), cyclolignolides (**174-178**), cyclolignans (**179-181**), and bisepoxylignans (**182-190**).

Simple lignans, which serve as the precursor structure for more complex lignans, are composed of two phenylpropanoid molecules linked by a carbon atom at the β position, specifically at C8-C8'. Secoisolariciresinol (**165**) and secoisolariciresinol-9,9'-acetonide (**164**) are simple lignans isolated from *D. giraldii* and *D. tangutica*, respectively. Monoepoxylignans (**166-173**) are formed by the condensation of hydrocarbon groups with oxygen-containing substituents at various positions, resulting in monoepoxide structures such as 7-O-7', 7-O-9', or 9-O-9' furan or tetrahydrofuran. A total of seven monoepoxylignans have been identified in *C. Daphnes*. Among these, four compounds feature a 9-O-9' structure, while three compounds exhibit a 7-O-9' structure. Monoepoxylignans of the 7-O-7' type have not been identified.

To date, nine bisepoxylignans (**182-190**) have been identified. These compounds are formed through the linkage of two phenylpropanoid side chains, resulting in the formation of two epoxy structures, specifically those with a bicyclic tetrahydrofuran ring. The skeleton of these compounds typically contains four chiral carbons, leading to the formation of diastereoisomers. The structures of these compounds are depicted in Figure 9.

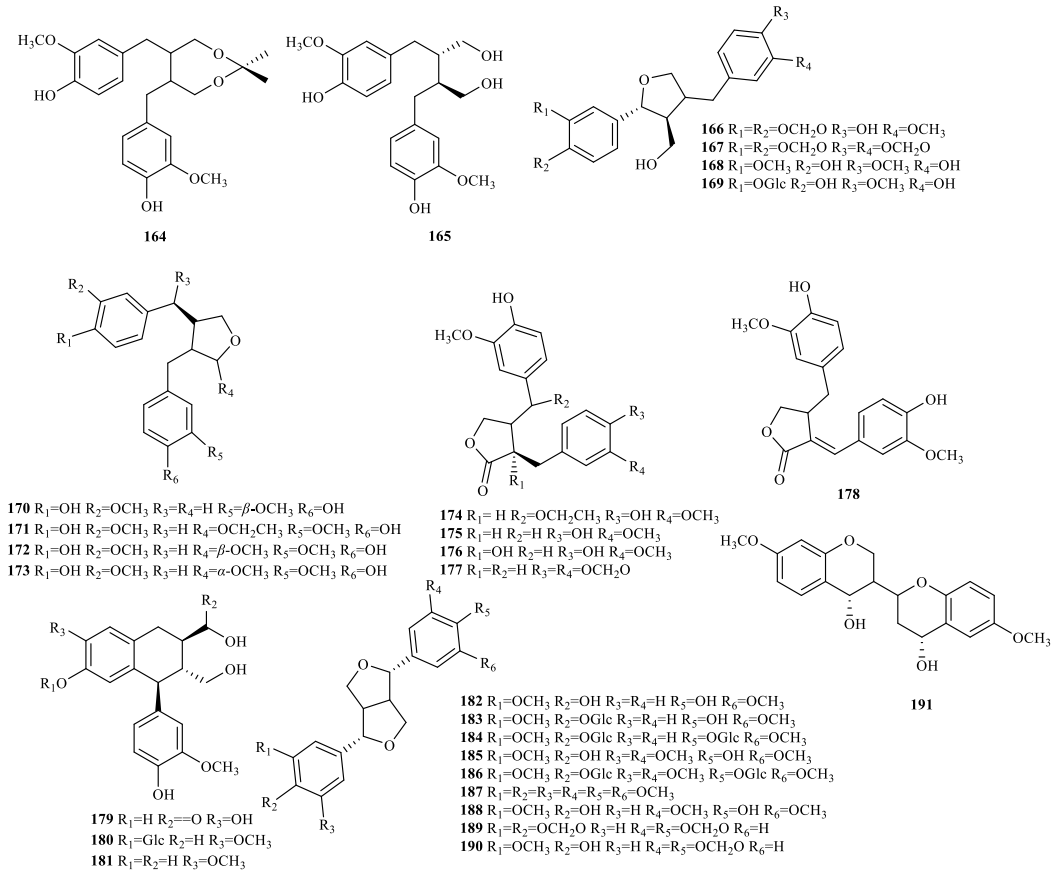

Figure 9. The structures of lignans (**164-190**) isolated from *C. Daphnes*

3.3. Terpenoids Compounds

Diterpenoids are abundantly present in *C. Daphnes*. In recent years, 64 terpenoid compounds have been isolated from *C. Daphnes*, which include 58 sesquiterpenes (**193-250**), an α-violet ketone-type monoterpene (**192**), and 5 pentacyclic triterpenes (**251-255**).

Most of these compounds were isolated from *D. tangutica* and *D. giraldii*. In contrast, only four compounds have been identified from *Daphne retusa*. Guo et al. [73] isolated an α-violet ketone-type monoterpene, Byzantionoside B (**192**), from the whole plant of *D. tangutica*.

Guo et al. [73] isolated 20 guaiane-type sesquiterpenoid compounds from *D. tangutica*, designated tanguticatin A-L. Additionally, using LC-MS/MS analysis and GNPS molecular networking, they identified five previously undescribed daphnane diterpenoid compounds, named tanguticanine A-E. Compounds **250**, **241**, and **242** also exhibited cytotoxic effects by inducing apoptosis in cells. Tanguticanine E (**242**) demonstrated an IC_{50} value of 9.93 ± 0.10 μM against HepG2 cells [74].

Wang et al. [75] isolated three diterpene protoacid ester compounds from *D. giraldii*. Among these, Daphnegiraldicin (**232**) is a novel diterpene protoacid ester isolated from this plant. The structural representations of these compounds are illustrated in Figure 10.

3.4. Other Compounds

Additionally, *C. Daphnes* contains other types of compounds, including sterols (**256-258**), organic acids (**259-267**), and phenolics (**268-279**). Yin et al. [6] identified an alkaloid, Aurantiamide acetate (**282**), from the stem of *D. tangutica*. Sun et al. [82] discovered a polysaccharide from the root bark of *D. giraldii*, which is composed of monosaccharides including mannose, glucosamine, rhamnose, glucose, galactose, arabinose, and fucose. The structures of these compounds are shown in Figure 11, and the substituents are depicted in Figure 12.

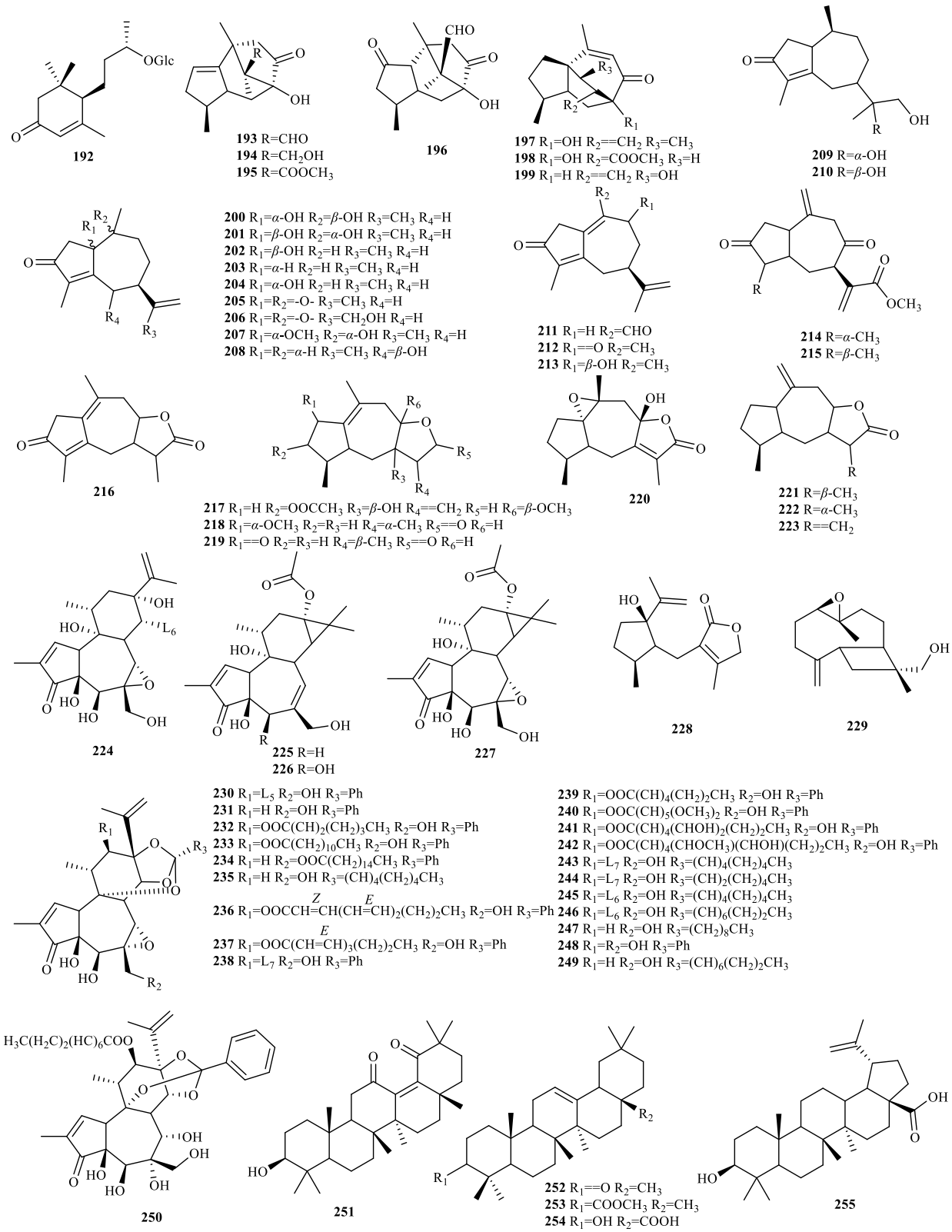

Figure 10. The structures of terpenoids (**192-255**) isolated from *C. Daphnes*

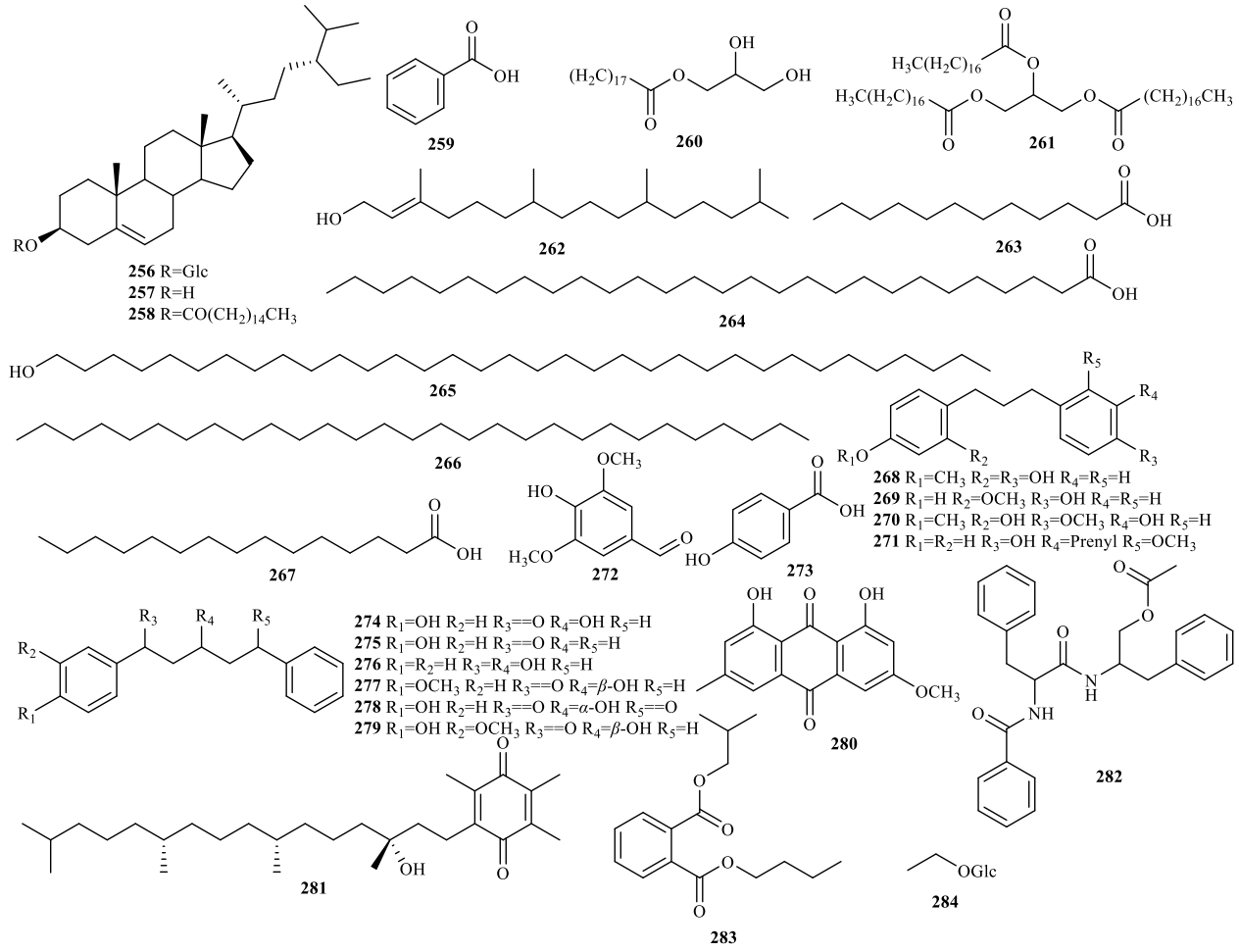

Figure 11. The structures of other compounds (**256-284**) isolated from *C. Daphnes*

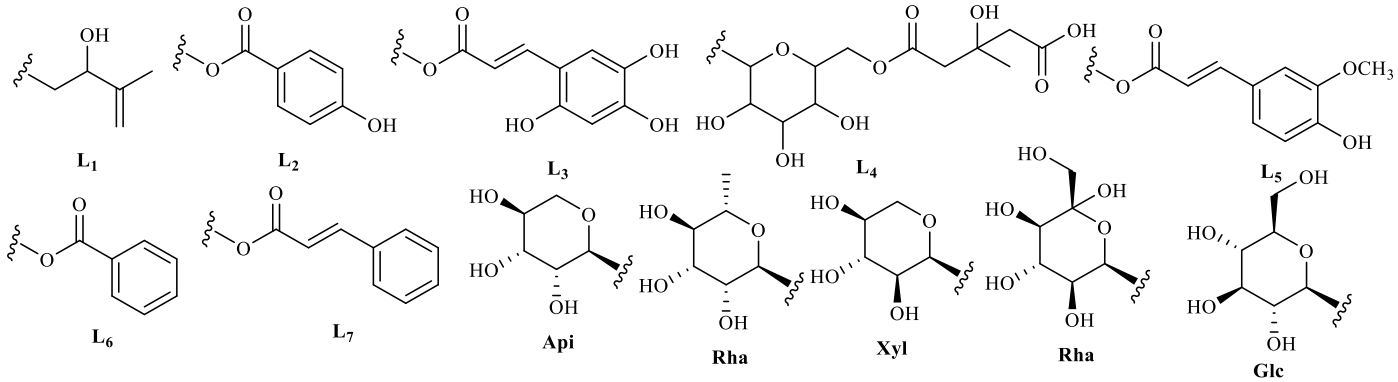

Figure 12. Structures of substitutes in *C. Daphnes*

4. Pharmacological Activities

In an era characterized by rapid advancements in research, the biological activities of various compounds have been rigorously investigated. Extracts and monomeric compounds derived from *C. Daphnes* have demonstrated potential therapeutic applications, including anti-tumor, immunomodulatory, antibacterial, antiviral, anti-hypoxic, and neuroprotective effects, as illustrated in Figure 13. Therefore, this paper endeavors to provide a comprehensive review and analysis of the pharmacological effects of *C. Daphnes* extracts and their functional monomers, as detailed in Table 4.

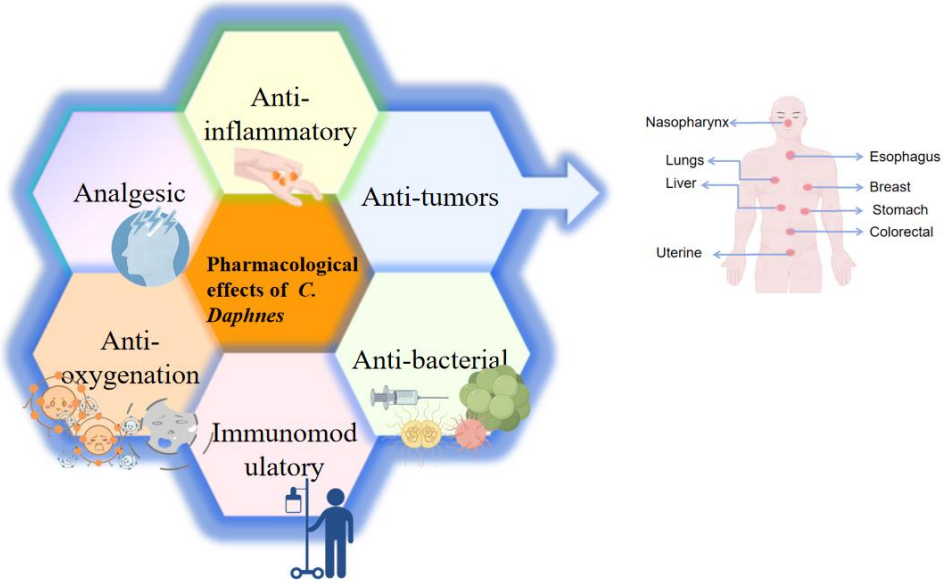

Figure 13. Pharmacological actions of *C. Daphnes*

4.1. Anti-inflammatory Effects

Inflammation is a natural physiological response of the body to external stimuli or injury, characterized by a complex series of processes. The literature identifies phenylpropanoids and flavonoids as the primary anti-inflammatory active components in *C. Daphnes*. These compounds are believed to exert their anti-inflammatory effects through the inhibition of inflammatory mediator release, the reduction of inflammatory cell infiltration and activation, and the modulation of inflammation-related pathways [83].

Research has identified the ethyl acetate extract of *C. Daphnes* [84] as a key agent exhibiting significant anti-inflammatory activity. Its mechanism of action included the inhibition of inducible nitric oxide synthase (iNOS) gene and protein expression within the MAPK/ERK signaling pathway. This inhibition reduced the production of interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and nitric oxide (NO), while simultaneously increasing haem oxygenase (HO)-1 levels. These actions contributed to regulating the body's internal environment and stabilizing the inflammatory state. Experimental results demonstrate that the aqueous extract of *C. Daphnes*, when processed with liquorice, effectively modulates the TLR4/NF-κB/NLRP3 signaling pathway [85]. As a result of this modulation, decreased levels of TNF-α, IL-6, IL-1β, matrix metalloproteinase (MMP)-1, MMP-3, and

vascular endothelial growth factor (VEGF) were observed both in vivo and in vitro. Additionally, an elevation in IL-10 levels was observed, significantly attenuating the inflammatory response in bovine type II collagen and Complete Freund's Adjuvant (CFA)-induced rheumatoid arthritis rats, as well as in lipopolysaccharide (LPS)-induced Raw264.7 cells.

Additionally, extracts from the bark and leaves of *C. Daphnes* [86] demonstrated significant inhibitory effects on the early stages of inflammation by suppressing exudation and edema. These extracted significantly inhibited the inflammatory response in rats with paw edema and mice with ear oedema.

Literature indicated that coumarins and flavonoid compounds from *C. Daphnes* [87] were its primary anti-inflammatory constituents. The total coumarins of *C. Daphnes* exhibited significant inhibitory effects on edema induced by egg albumin and xylene in rats. Furthermore, a clear dose-response relationship was observed between the inhibitory effect and the administered dose. Additionally, research by Li et al. [88] found that the total coumarins and flavonoids of *C. Daphnes* also exhibited inhibitory effects on the swelling in the same experimental models.

Daphnetin (**114**) had been shown to effectively downregulate NF-κB activity in LPS-induced macrophages and human alveolar epithelial cells. This downregulation occurs through the modulation of non-degradative TRAF6 ubiquitination, which subsequently inhibits inflammatory responses [89]. Additionally, daphnetin (**114**) also exhibited anti-inflammatory effects in rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS). It not only inhibited the expression of inflammatory cytokines such as IL-6, TNF-*α*, and Bcl-2, but also activated the PERK/ATF4/CHOP signaling pathway, leading to the upregulation of PERK, GRP78, and caspase-12 [90]. This activity is associated with endoplasmic reticulum stress, which promotes the apoptosis of RA-FLS [91]. Furthermore, daphnetin (**114**) modulated the MAPK [92] and JAK/STAT [93] pathways to suppress the activation of LPS-induced glial cells and RAW264.7 cells, thereby reducing ERK protein phosphorylation levels and balancing intracellular inflammatory responses. Moreover, daphnetin (**114**) [94] inhibited the proliferation of HaCaT cells and the release of the inflammatory cytokine CCL20, demonstrating significant therapeutic effects on psoriasis-like dermatitis.

Daphnin (**117**) has been shown to reduce joint swelling in collagen-induced arthritis (CIA) mice by modulating the T helper (Th)17/Treg cell imbalance and reducing TNF-*α* levels [8]. Luteolin (**9**) [95] inhibited NF-κB phosphorylation and prevented cartilage degradation in rats. Additionally, genkwanin (**6**) [96] exhibited anti-inflammatory effects by inhibiting the activation of the JAK/STAT and NF-κB pathways, and suppressing xylene-induced ear swelling in mice. Umbelliferone (**122**) [97] exhibited potent analgesic and anti-inflammatory activity by inhibiting pain mediators at both peripheral and central levels. After four treatments, it demonstrated a 46.28 % and 66.13 % reduction in acetic acid-induced edema. Daphnoretin (**151**) [98] demonstrated inhibitory effects on the secretion of inflammatory cytokines in cells. At a concentration of 1 μg/mL, it significantly suppressed the secretion of the inflammatory factors monocyte chemoattractant protein-1 (MCP-1) and IL-1*β*. Furthermore, at concentrations above 10 μg/mL, it significantly inhibited the secretion of the inflammatory factor TNF-*α*. Osthole (**128**) [99] downregulated the expression of APOE and TREM2 proteins and genes induced by Aβ1-42 in BV2 cells, showing a favorable therapeutic effect on inflammatory responses. Additionally, it exhibited a protective effect against LPS-induced mastitis in mice [100] and inflammation-induced damage in the substantia nigra of rats [101].

4.2. Anti-tumors Effects

Tumors develop when cells in local tissues lose normal growth regulation at the genetic level, often as a result of various carcinogenic factors, leading to abnormal proliferation and the formation of neoplastic tissues. Research suggested that *C. Daphnes* and its extracted may serve as potential therapeutic agents against tumors through various mechanisms, including anti-proliferation, induction of apoptosis, inhibition of angiogenesis, and modulation of the immune response [102] .

Daphnetin (**114**) [103] demonstrated dose-dependent inhibition of proliferation and viability in human malignant melanoma cell lines (FM55P, A375, FM55M2, and SK-MEL28), with IC_{50} values ranging from 40.48±10.90 μM to 183.97±18.82 μM. At a high concentration (10 μg/mL), it [9] inhibited the activation of the MAPK/STAT3/NF-κB pathway, reduced the levels of the pro-inflammatory factor IL-18 in lung adenocarcinoma A549 cells, and subsequently inhibited cell proliferation, colony formation, migration, and invasion. In vitro, the MTT assay demonstrated that daphnetin (**114**) [104] inhibited MCF-7 and MDA-MB-231 breast cancer cells, with IC_{50} values of 2.0 and 1.0 μM, respectively. This inhibition was associated with a significant increase in the levels of p21, Bcl-2-associated X protein (Bax), and cleaved caspase-9 and -3. It also decreased the levels of cyclin E, cyclin-dependent kinase 2 (CDK2), and Bcl-2, leading to cell cycle arrest in the S phase and induction of apoptosis, thereby inhibiting the proliferation of breast cancer cells. Additionally, studies have shown that daphnetin (**114**) also had significant therapeutic effects on liver cancer cells such as Huh7 and SK-HEP-1 [105], esophageal squamous cell carcinoma (ESCC) cells [106], and endometrial cancer cells (HEC-1B) [107], among others.

Ma et al. [108] demonstrated that lariciresinol (**168**) inhibited cell proliferation and induced S phase cell cycle arrest, subsequently leading to apoptosis in HepG2 cells. Meanwhile, genkwanin (**6**) [109] at concentrations of 0, 10, 30, 60, 90, and 120 μM significantly inhibited the proliferation of two human colon cancer cell lines, HT-29 and SW-480, as well as the production of inflammatory cytokines IL-8, IL-1α, IL-1β, and IL-6 in vitro in a concentration-dependent manner. In vivo, APC (Min/+) mice treated orally with genkwanin (**6**) at doses of 12.5 and 25 mg/kg/day showed a significant improvement in the secretion of several immune-related cytokines, including IL-2, IL-4, IL-12, interferon (IFN)-γ, and TNF-*α*. These results suggested that genkwanin (**6**) inhibited colon cancer cell proliferation by enhancing host immunity and reducing inflammatory cytokines. Additionally, daphnegiravone B (**23**) [36] exhibited inhibitory effects on U251, A549, HepG2, MCF-7, and Bcap37 cell lines, with IC_{50} values ranging from 4.26 to 20.82 μM. Daphnegiravone D (**22**) [110] and daphnegiralin K (**83**) [111] significantly induced apoptosis in Hep3B cells, with the former increasing apoptosis and reactive oxygen species (ROS) production in Hep3B cells. The latter was associated with the upregulation of Bax and cleaved PARP (cl-PARP) expression and inhibition of Bcl-2 expression. The apoptosis rates of Hep3B cells treated with different concentrations of compound **39** (5, 10, 20 μM) were 14.85 %, 61.63 %, and 88.76 %, respectively. Umbelliferone (**122**) [112] increased the levels of Bax in both A427 and Calu-1 lung cancer cells but inhibited Bcl-2 levels only in A427 cells. Consequently, the anti-proliferative effects on A427 cells were stronger than those on Calu-1 cells, with growth inhibition rates (GI%) of 54.00±0.13 and 30.00±0.17, respectively. The compounds daphnegiranol C1 (**49**)/C2 (**50**) and daphnegiranol D1 (**51**)/D2 (**52**) [49] exerted inhibitory effects on three hepatocellular carcinoma cell lines (Hep3B, MHCC97H, HepG2). The latter two induced apoptotic cell death by increasing ROS levels in the cells. Daphnoretin (**151**) [113] inhibited macrophage polarization towards the M2 phenotype, thereby influencing mitochondrial pathway expression in rats and promoting apoptosis in nasopharyngeal carcinoma cells. Additionally, osthole

(**128**) [114] arrested N87 cells at the G2/M phase via the caspase-3 signaling pathway, thereby inhibiting N87 cell proliferation.

4.3. Anti-bacterial Effects

Infectious diseases caused by various pathogenic strains continue to be a leading cause of mortality and morbidity worldwide [115]. Coumarin compounds have been demonstrated to reduce bacterial pathogenicity and drug resistance by inhibiting the bacterial quorum sensing system, which in turn decreased the expression of associated virulence factors and inhibited biofilm formation. Different extracts of *C. Daphnes* [10], including water, 75 % methanol, and 75 % ethanol, exhibited significant inhibitory effects on three plant pathogens: *Fusarium graminearum* Schw. (FGS), *Helminthosporium sorokinanum* Sacc. (HSS), and *Rhizoctonia cerealis* Vander Hoeven (RCVH). The study also compared different extraction solvents, times, and temperatures, finding that the antibacterial effect was most pronounced when *Cortex Daphnes* was extracted with 75 % ethanol at 70 °C for 1 h. Among these pathogens, FGS and RCVH exhibited the strongest antibacterial activity, with a minimum inhibitory concentration (MIC) of 1/256. The antibacterial effect against HSS was weaker, with an MIC of 1/128. Meanwhile, an aqueous extract of *C. Daphnes* [116] demonstrated inhibitory effects against seven pathogens, including tomato wilt and cucumber anthracnose. The inhibitory effect on cucumber target spot and strawberry red intermediate central pillar was the strongest among all extracts, with EC_{50} values of 0.925 and 0.920 mg/mL, respectively. Zhao [117] utilized both the test tube method and viable count method to assess the in vitro antibacterial activity of *C. Daphnes* injection. Both methods showed antibacterial activity against *Staphylococcus aureus*, while the latter was also employed to determine activity against *Escherichia coli*. Furthermore, Ye et al. [118] found that *C. Daphnes* essential oil exhibited diverse antibacterial effects on various bacteria tested using the two-fold dilution method. Among these, *Staphylococcus aureus* and *Bacillus subtilis* were particularly sensitive, exhibiting the most potent antibacterial effects, with an MIC of 1/256. The MIC values for *Saccharomyces cerevisiae*, *Aspergillus flavus*, and *Aspergillus niger* were all 1/128. However, it exhibited the weakest antibacterial activity against *Escherichia coli*, with an MIC of only 1/32.

Daphnetin (**114**) [119], both in vivo and in vitro, had been shown to facilitate biofilm formation in methicillin-resistant *Staphylococcus aureus* (MRSA), disrupt bacterial cell walls, and increase MRSA's susceptibility to antimicrobial agents, thereby contributing to the mitigation of MRSA resistance. Concurrently, it [120] exhibited a significant concentration-dependent inhibitory effect on the growth of *Ralstonia pseudosolanacearum*, with a MIC of 75 mg/L. In their study, Zhou et al. [121] demonstrated that Daphnetin (**114**) significantly enhanced macrophage phagocytic activity against bacteria, markedly upregulated the expression of antimicrobial factors like IL-22, and inhibited the expression of inflammatory cytokines IL-1β, TNF-α, and IL-6 induced by *Staphylococcus aureus* infection. This confers a protective effect against *Staphylococcus aureus* infections. In vitro experiments indicated that Daphnoretin (**151**) [122] exhibited strong inhibitory activity against *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, with a MIC of 20 mg/mL.

4.4. Immunomodulatory Effects

Reportedly, Daphnetin (**114**) [11] exhibited immunomodulatory activity by significantly inhibiting both humoral and cell-mediated immune responses, while enhancing the phagocytic activity of phagocytes in vivo. Consequently, it acted as an effective immunomodulator. In experimental autoimmune encephalomyelitis (EAE) mice, Daphnetin (**114**) demonstrated notable therapeutic efficacy through two primary mechanisms. Firstly [123], it effectively reduced the numbers of Th1 and Th17 cells and inhibited the expression of pro-inflammatory cytokines, including IFN-γ, signal transducer and activator of transcription (STAT)-4, STAT3, T-box expressed in T cells (T-bet), IL-17, retinoic acid receptor-related orphan receptor (ROR)-γt, and TNF-*α*. Concurrently, it upregulated the proportions of Th2 and Treg cells and increased the levels of anti-inflammatory cytokines such as IL-4, IL-10, transforming growth factor (TGF)-*β*, and IL-33, thereby achieving therapeutic outcomes. Secondly [124], Daphnetin (**114**) exerted therapeutic effects by elevating the levels of heme oxygenase-1 (HO-1) and reduced the levels of malondialdehyde in mice, thereby further enhancing its therapeutic efficacy. Additionally, in BALB/c mice sensitized with OVA, intraperitoneal injection of Daphnetin (**114**) [125] at doses of 5, 10, and 20 mg/kg for 28 consecutive days resulted in decreased levels of serum immunoglobulin G (IgG), IgG1, IgG2b, Th1, and Th2. This observation suggested that Daphnetin could suppress humoral immune response activity in OVA-sensitized mice. Furthermore, Daphnetin (**114**) [126] ameliorated the imbalance of Th17 and Treg cell-related cytokines in the peripheral blood mononuclear cells and decidual tissues of recurrent spontaneous abortion (RSA) mice, and restored damaged decidual cells in the decidual tissues of RSA model mice. It also enhanced angiogenesis and vascular cell integrity, promoting immune regulation in these mice. Meng's research [127] demonstrated that Daphnetin (**114**) could increase the levels of $CD4^+$ cells at specific doses, thereby achieving anti-immune rejection. Additionally, it [128] significantly inhibited immunoglobulin levels, reduced the production of immune cell cytokines, and consequently decreased the proliferation rate of splenic cells.

Genkwanin (**6**) [107] also improved body weight, spleen and thymus indices, as well as immune cell cytokine secretion in APC (Min/+) mice, thereby enhancing the immune competence of these mice. Research by Shi et al. [129] demonstrated that five compounds, including umbelliferone (**122**), daphnin (**117**), daphnoretin (**151**), genkwanin (**6**), and daphnodorin B (**94**), at a concentration of 20 mg/L, significantly enhanced the secretion of IL-1 and IL-2 in mouse cells. However, at a concentration of 30 mg/L, this enhancing effect diminished. This suggested that these compounds exhibited immunomodulatory effects in mice, with their activity being dependent on the chemical structure. Specifically, a higher number of phenolic hydroxyl groups in the compound correlates with a stronger effect.

4.5. Anti-oxygenation Effects

The methanol extract of *C. Daphnes* [12] significantly attenuated cortical neuronal cell damage induced by glutamate (L-glutamate), kainic acid (KA), and hydrogen peroxide (H_2O_2) in rats. Additionally, the extract demonstrated a strong ability to inhibit lipid oxidation [130]. The ethyl acetate extract of *C. Daphnes* [83] inhibited iNOS gene and protein expression via the MAPK/ERK signaling transduction pathway, thereby reducing NO production in cells and further enhancing cellular antioxidant capacity.

Daphnetin (**114**) [131] exhibited strong scavenging activity via the SPLET mechanism in both aqueous and lipid environments. Daphnogirin A (**103**) and B (**104**) [53] demonstrated antioxidant properties by reducing the absorbance capacity of the test sample for peroxyl radicals, as indicated by

the quenching curve of fluorescein disodium. At a concentration of 50 μM, nortrachelogenin (**176**) [12] significantly reduced intracellular antioxidant levels, including glutathione and superoxide dismutase. It also attenuated cell damage induced by H_2O_2 and excitotoxic neurotransmitters (glutamate, kainic acid), but had no effect on neurotoxic damage induced by N-methyl-D-aspartate (NMDA). Luteolin (**9**) [132] inhibited the overexpression of pyroptosis-related genes and proteins, including NLRP3 and caspase-1, in splenic lymphocytes exposed to ammonia, thereby exerting antioxidant effects on the lymphocytes.

4.6. Analgesic Effects

Daphnetin (**114**) [133] suppressed the expression of inflammatory cytokines (IL-1β, IL-6, TNF-α) and inhibited the activation of microglia, astrocytes, and neurons in the spinal cord of neuropathic pain (NP) rats. Additionally, it promoted the polarization of M1 microglia and A1 astrocytes towards the M2 and A2 phenotypes, respectively, thereby attenuating central sensitization induced by glial polarization and alleviating noxious sensitization in NP rats. Ye et al. [134] investigated the analgesic effects of Daphnetin (**114**) in various pain models in mice, including acetic acid-induced writhing, the hot plate test, and electrical stimulation. They found that Daphnetin (**114**) exhibited potent analgesic effects in mice subjected to acetic acid-induced writhing and the hot plate test, but its efficacy was less pronounced in the electrical stimulation model. Additionally, they observed that the analgesic efficacy of Daphnetin increased with higher concentrations. Zhang et al. [135] demonstrated that Daphnetin (**114**) reduced pain and protects nerves by modulating the expression of chemokines, including CXCL13/CXCR5, and by influencing neuroglial cell polarization.

Liu et al. [136] found that luteolin (**9**) (1 mg/kg/day) administered via gavage significantly prolonged the latency (pain threshold) in mice, while reducing the number of twitches and the suppression rate of the response at 10 and 20 min, with suppression rates of 30 % and 25 %, respectively. In other studies, luteolin significantly alleviated neuropathic pain in mice by activating GABAA receptors and μ-opioid receptors in the spinal cord, thereby reducing mechanical and cold pain. Osthole (**128**) [137] demonstrated analgesic effects in rats with bone cancer pain, potentially by inhibiting the release of inflammatory factors and the activation of spinal cord microglia via the TLR4/NF-κB signaling pathway.

4.7. Other Effects

In addition, *C. Daphnes* exhibited neuroprotective properties, aids in obesity management, thrombus formation inhibition, and antiviral activity.

Alterations in synaptic morphology and structure, such as increased synaptic vesicle density, are closely associated with improvements in learning and memory. High-pressure electron tomography revealed that the umbelliferone (**122**) [138] group exhibited increased synaptic vesicle density and a significant rise in the number of synaptic vesicles compared to the scopolamine group. Daphnetin (**114**) [139] enhanced autophagy in the brains of Alzheimer's disease (AD) mice by upregulating LC3-II and Beclin-1 protein expression while inhibiting p62 protein expression. This enhancement of cellular autophagy contributed to the amelioration of learning and memory deficits in the AD mouse model. Cichoriin (**113**) [140] upregulated PPAR-γ mRNA and protein expression, thereby

ameliorating metabolic disturbances induced by a high-fat diet (HFD) in obese rats. It also improved the physiological characteristics of various tissues, including the heart and liver. Furthermore, this compound [141] ameliorated the pathological features of HFD/streptozotocin-induced diabetic rats. Yusa et al. [142] demonstrated that Daphnodorin A (**93**), B (**94**), and C (**95**) exhibited anti-HIV-1 activity by inhibiting viral replication, significantly suppressing peripheral lymphocyte formation. Ho [143] discovered that daphnetin (**114**) exhibited anti-RSV activity with an IC_{50} of 5.87 μg/mL. Meanwhile, it ameliorated glucocorticoid-induced hyperuricemia in rats. Daphnetin (**114**) [144] significantly inhibited platelet aggregation and accumulation in rabbits. Additionally, it played a critical role in platelet function by regulating cPLA2 phosphorylation, thereby suppressing TxA2 generation.

Table 4. Pharmacological Activities of *C. Daphnes*

Effects	Pathway	Effective compounds or fraction	Vitro or vivo	Models	Dosage	Impact Factor	Ref.
Anti-inflammatory	-	Daphnoside (**115**)	In vivo	Collagen-induced arthritis (CIA) mice	2, 4, 8 mg/kg	↓IL-1*β*, IL-17, TNF-*α*, Treg↑Th17	[8]
	MAPK/ ERK	Ethyl acetate extract of *C. Daphnes*	In vitro	IFN and LPS-induced RAW264.7 cells	50, 100, 200 mg/L	↓IL-1*β*, IL-6, TNF-*α*, iNOS↑HO-1	[84]
	TLR4/ NF-κB/ NLRP3	Aqueous extract of *C. Daphnes*	In vivo	Rheumatoid arthritis rats induced by bovine type II collagen and Freund's complete adjuvant	0.1215, 1.0486 mg/mL	↓TNF-*α*, IL-6, IL-1*β*, MMP-1, MMP-3, VEGF, TLR4, NLRP3, NF-κB↑IL-10	[85]
			In vitro	LPS-induced Raw264.7 cells	0.06, 0.14 mg/mL	↓IL-1*β*, IL-6, TNF-*α*, TLR4, NF-κB	
	-	Bark and leaves of *C. Daphnes*	In vivo	Foot-swollen rats and ear-swollen mice	30, 60, 120 mg/kg	-	[86]
	-	Total coumarins of *C. Daphnes*	In vivo	Foot-swollen rats and ear-swollen mice	10, 20, 40 mg/kg	-	[87]
	-	Total coumarins and flavone of *C. Daphnes*	In vivo	Foot-swollen rats and ear-swollen mice	30, 60, 120 mg/kg	-	[88]
	NF-κB	Daphnetin (**114**)	In vitro	LPS-induced macrophages and human alveolar epithelial cells	5, 10 mg/kg	↓NF-κB	[89]

PERK/ ATF4/ CHOP	Daphnetin (**114**)	In vitro	Rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS)	0, 5, 10, 20, 30, 40, 50, 60, 70mg/L	↓IL-6, TNF-*α*, Bcl-2↑PERK, p-PERK, ATF4, GRP78, CHOP, Caspase-12	[90]
ERS	Daphnetin (**114**)	In vitro	Rheumatoid arthritis fibroblast-like synoviocytes	0, 10, 20, 30, 40, 50, 60, 70 mg/L	↑ERK	[91]
MAPK/NF-κB/ NLRP3	Daphnetin (**114**)	In vitro	LPS-induced MLE-12 cells	0, 5, 10, 20 μg/mL	↓IL-1*β*, IL-18, IL-6, iNOS↑CD38	[92]
JAK/ STATs	Daphnetin (**114**)	In vitro	LPS-induced Raw264.7 cells	5 mg/kg	↓TNF-*α*, IL-1*β*, IL-6, NO, PGE2, iNOS, COX-2, ROS	[93]
NF-κB	Daphnetin (**114**)	In vivo	Psoriasis mice	0.1 mg	↓V*γ*4+ T lymphocytes, IL-17A, IFN-*γ*, CXCL8, IL-23	[94]
		In vitro	HaCaT cells	20 μM	↓CCL20, IL-8, TNF-*α*	
-	Luteolin (**9**)	In vitro	Rat chondrocytes	0.25, 50, 100 μM	↓NO, PGE2, TNF-*α*, MMP-2, MMP-8, MMP-9, COX-2, iNOS, MMP-1, MMP-3, MMP-13	[95]
JAK/ STAT/ NF-κB	Genkwanin (**6**)	In vivo	adjuvant-induced arthritis (AIA) rats	5, 10, 20 mg/kg	↓TNF-*α*, IL-6, NO↑IL-10	[96]
-	Umbelliferone (**122**)	In vivo	Acetic acid-induced rats	5, 10 mg/kg	-	[97]
-	Daphnoretin (**151**)	In vitro	THP-1 cells	1, 10, 20, 50, 80, 100 μg/mL	↓TNF-*α*, MCP-1, IL-1*β*, IL-6	[98]
APOE-TREM2	Osthole (**128**)	In vitro	Aβ1-42-induced BV2 cells	1, 5, 25 mmol/L	↓TNF-*α*, IL-1*β*, APOE, TREM2	[99]
-	Osthole (**128**)	In vivo	LPS-induced mouse mastitis	20, 30, 40 mg/kg	↓NO, MDA, MPO, IL-1*β*, IL-6, TNF-*α*↑T-SOD, GSH-PX, CAT	[100]
-	Osthole (**128**)	In vivo	Striatum-	82	↓CXCL1,	[101]

				inflamed rats	mmol/L	CXCR2	
	MAPK/ STAT3/ NF-κB	Daphnetin (**114**)	In vitro	Lung adenocarcinoma A549 cells	0, 5, 10μg/mL	↓IL-18, IL-1*β*, iNOS, p-STAT3, p-NF-κB p105, p-NF-κB p65, p-IκB	[9]
	-	Daphnegiranol C1 (**49**)/C2 (**50**), Daphnegiranol D1 (**51**)/D2 (**52**)	In vitro	Hep3B, MHCC97H, HepG2 cells	5 μM	↑ROS	[49]
	-	Daphnetin (**114**)	In vitro	Malignant melanoma	2, 10, 20, 40, 50, 60, 100, 150, 200 μM	-	[103]
	PI3K/ AKT	Daphnetin (**114**)	In vitro	Breast cancer MCF-7 and MDA-MB-231 cells	0.5, 1, 2, 4, 6, 8 μM	↑p21, Bax↓Cyclin E, CDK2, Bcl-2, p-PI3K/PI3K, p-AKT/AKT	[104]
	Wnt/*β*-catenin	Daphnetin (**114**)	In vitro	Huh7 and SK-HEP-1 cells	0, 5, 10, 50, 100 μM	↓β-catenin	[105]
	-	Daphnetin (**114**)	In vitro	Esophageal cancer cells	-	↑TAC, MDA, SOD	[106]
Anti-tumors	-	Daphnetin (**114**)	In vitro	HEC-1B cells	25, 50, 75, 100, 200 μmol/L	↓Ki-67, CK7, Cerb B-2 m RNA↑TP53	[107]
	-	Lariciresinol (**168**)	In vitro	HepG2 cells	50, 100, 200, 400, 800 μg/mL	↓Bcl-2↑Bax, PARP, Caspase-3,9	[108]
	-	Genkwanin (**6**)	In vitro	Human colorectal cancer HT-29 and SW-480 cells	0, 10, 30, 60, 90, 120 μM	↓IL-1*α*, IL-1*β*, IL-6, IL-8, G-CSF, GM-CSF	[109]
	-	Daphnegiravone D (**22**)	In vitro	Hep3B cells	0, 0.5, 1, 2 μM	↑ROS	[110]
	-	Daphnegiralin K (**83**)	In vitro	Hep3B cells	5, 10, 20 μM	↑Bax, cl-PARP↓Bcl-2	[111]
	-	Umbelliferone (**122**)	In vitro	A427 and Calu-1cells	1 μM	↓Bcl-2↑Bax	[112]
	-	Daphnoretin (**151**)	In vivo	Nasopharyngeal carcinoma rats	24 mg/kg	↓Bcl-2, CD163↑Bax, Cyto-C, CD68	[113]
	Caspase-3	Osthole (**128**)	In vitro	Gastric cancer N87 cells	50, 100 mg/kg	↓Cyclin B1, Bcl-2, Bcl-xL↑Bax,	[114]

						Caspase-3	
	-	*C. Daphnes* extract	In vitro	Fusarium graminearum Schw.,Helmintho-sporium sorokinanum Sacc., Rhizoctonia cerealis Vander Hoeven	0.078125, 0.15625, 0.3125, 0.625, 1.25, 2.5, 5, 10, 20 mg/m L	-	[10]
	-	Aqueous extract of *C. Daphnes*	In vitro	Cucumber target spot, strawberry red core, eggplant wilt, cucumber wilt, cucumber anthracnose, tomato wilt, chili wilt	0.25, 0.5, 1, 2, 4, 8 mg/mL	-	[116]
	-	*C. Daphnes* injection	In vitro	Escherichia coli, Staphylococcus aureus	0.03925, 0.0785, 0.157 mL	-	[117]
Anti-bacterial	-	*C. Daphnes* essential oil	In vitro	Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Penicillium sp., Aspergillus sp., Saccharomyces cerevisiae	-	-	[118]
	-	Daphnetin (**114**)	In vitro	Methicillin-resistant Staphylococcus aureus	16, 32, 64, 128, 256, 512 μg/mL	-	[119]
	-	Daphnetin (**114**)	In vitro	Ralstonia pseud solanacearum	50, 100 mg/ L	-	[120]
	-	Daphnetin (**114**)	In vitro	Staphylococcus aureus	10, 20, 40, 80, 160 μM	↑IL-22, Reg-3β, S100A8, Miz1↓1L-1*β*, TNF-*α*, 1L-6	[121]
	-	Daphnoretin (**151**)	In vitro	Group B Streptococcus, Streptococcus pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli	20 mg/mL	-	[122]

	-	Daphnetin (**114**)	In vivo	Experimental autoimmune encephalomye-litis (EAE) mice	2, 8 mg/kg	↑IL-4, IL-10, IL-33, GATA3, TGF-*β*, FoxP3↓IFN-*γ*, STAT4, T-bet, IL-17, STAT3, ROR-γT, TNF-*α*	[123]
	-				8 mg/kg	↓IL-17, IFN-*γ*, IL-6, IL-12a, IL-23a, IL-1*β*, TNF-*α*↑HO-1	[124]
	-	Daphnetin (**114**)	In vivo	OVA-induced BALB/c mice	5, 10, 20 mg/kg	↓IgG, IgG1, IgG2b, Th1, Th2	[125]
	-	Daphnetin (**114**)	In vivo	Recurrent spontaneous abortion (RSA) mice	1, 4 mg/kg	↓IL-2, Th17, Foxp3, STAT3↑IL-6, Treg, RORγt, STAT5	[126]
Immunomodulat-ory	-	Daphnetin (**114**)	In vivo	Heart heterotopic transplantation rats	4 mg/kg	↑CD4+CD25+Foxp3+Treg	[127]
	NF-κB	Daphnetin (**114**)	In vivo	Mouse lymphocyte	2, 4, 8, 16, 32, 64 μmol/L	↓ IL-2, IFN-γ, IL-4, IL-6	[128]
	-	Umbelliferone (**122**), Daphnin (**117**), Daphnoretin (**151**), Genkwanin (**6**), Daphnodorin B (**94**)	In vitro	Mouse macrophages, T lymphocytes	20, 30 mg/L	↓IL-1*β*, IL-2	[129]
	-	Daphnetin (**114**)	In vivo	-	-	↑ HO, HOO, NO2	[130]
	-	Nortrachelogenin (**176**)	In vitro	H_2O_2-induced cells	50 μM	↑SOD, GSH-Px	[12]
	-	Daphnogirin A (**103**), Daphnogirin B (**104**)	In vitro	-	312.5 ng/mL	-	[53]
Anti-oxidant	-	*C. Daphnes* polysaccharide	In vitro	-	0 ~ 2 mg/mL	-	[82]
	-	Ethyl acetate extract of *C. Daphnes*	In vitro	IFN and LPS-induced RAW264.7 cells	100, 200 mg/L	↓NO, iNOS	[84]
	-	Luteolin (**9**)	In vitro	Chicken splenic lymphocytes	100 μL	↓LDH, MDA↑ROS,	[132]

						SOD, GSH-Px	
	-	Daphnetin (**114**)	In vivo	Neuropathic pain rats	2.5, 5, 10, 20, 40 μg/mL	↓IL-1*β*, IL-6, TNF-*α*	[133]
	-	Daphnetin (**114**)	In vivo	Acetic acid, hot plate analgesiometer, electric stimulation-induced pain mice	25, 50 mg/kg	-	[134]
Analgesia	-	Daphnetin (**114**)	In vivo	Neuropathic pain rats	0.0625, 0.025 mg/kg	↓IL-1*β*, IL-6, TNF-*α*, TLR4, p-IKB*α*, NF-κB, GFAP, CXCL1, CXCR2	[135]
	-	Luteolin (**9**)	In vivo	Hot plate test mice	1 mg/kg	-	[136]
	TLR4/ NF-κB	Osthole (**128**)	In vivo	Bone cancer pain rats	10, 20 mg/kg	↓TNF-*α*, IL-1*β*, IL-6, TLR4, p-NF-κB	[137]
	-	Umbelliferone (**122**)	In vitro	Scopolamine-induced hippocampal damage	10 μM	-	[138]
Neuroprotection	-	Daphnetin (**114**)	In vivo	Alzheimer's disease (AD) mice	200 mg/kg	↑LC3-II, Beclin-1↓p62	[139]
	-	Cichoriin (**113**)	In vivo	High-fat diet (HFD)-induced obese rats	50, 100 mg/kg	↑PPAR-*γ*, AST, ALT↓TG, TC, LDL-C	[140]
Weight suppression	-	Cichoriin (**113**)	In vivo	High-fat diet/ streptozotocin-induced diabetic rats	50, 100 mg/kg	↓BG, TG, TC, MDA↑TAC, SOD, GLUT4, AMPK, PI3K	[141]
	-	Daphnodorin A (**93**), B (**94**), C (**95**)	In vitro	HIV-1	3 ~30 μg/mL	-	[142]
Anti-viral	-	Daphnetin (**114**)	In vitro	Respiratory syncytial virus (RSV)	7.81 μg/mL	-	[143]
Anti-thrombotic	-	Daphnetin (**114**)	In vitro	GPVI-mediated platelets	25, 50, 100 μM	↓TxA2, cPLA2, ERK	[144]

5. Clinical Application

Cortex Daphnes, commonly known as *Zu Shi Ma*, is characterized by its pungent taste and is effective in dispersing blood stasis, with notable analgesic properties. Additionally, due to its warm and pungent nature, it significantly disperses wind, eliminates dampness, warms the center, and dispels cold. It also soothes skin bruises, swelling, and conditions such as wind-cold-damp bi syndrome caused by external injuries, traditionally encapsulated in the saying "Da de mang di pa, li bu kai zu shi ma."

C. Daphnes is widely utilized in clinical practice for treating various conditions, including rheumatoid arthritis, diabetes, tumors, and infectious diseases. Clinical studies have demonstrated the favorable efficacy and safety of *C. Daphnes* in treating these conditions. For example, it can reduce pain and swelling in patients with rheumatoid arthritis, improve glycemic control in diabetics, inhibit tumor growth and metastasis, and combat infectious diseases. Numerous formulations containing *C. Daphnes* and related preparations are also widely used in traditional medicine.

5.1. Arthritic Diseases

Arthritis is a prevalent chronic condition that substantially impairs patients' quality of life [145-146]. As a traditional herbal remedy, *Zu Shi Ma* has been shown to effectively alleviate pain and inflammation in arthritis patients, improve joint function, and demonstrate favorable safety and tolerability profiles. It is widely employed in the treatment of arthritis within the clinical practice of traditional Chinese medicine. The combination of *Zu Shi Ma Pian* and meloxicam [16] has been shown to alleviate knee joint pain and demonstrate favorable efficacy in the acute phase of knee osteoarthritis treatment, with an overall efficacy rate of 96.8% in the treatment group. The combined treatment of acupuncture and *Zu Shi Ma* [147] effectively relieves pain, improves joint function in knee osteoarthritis patients, and reduces the incidence of adverse effects. *Zu Shi Ma Pian* [148] can also be combined with nimesulide for the treatment of osteoarthritis. Following treatment, serum levels of IL-1β, MMP-3, and CTX-II were significantly reduced, and treatment efficacy increased by 17.5 % compared to patients taking oral nimesulide alone. Additionally, *Zu Shi Ma Pian* [149] demonstrated therapeutic effects in patients with rheumatoid arthritis, with a Traditional Chinese Medicine syndrome efficacy rate of 94 %. Treatment of 40 patients with wrist joint lesions due to cold-damp obstructive type rheumatoid arthritis using *Zu Shi Ma Gao Yao* [150] resulted in a clinical cure rate of 55.00 %. In contrast, indomethacin patches used to treat 20 patients with bilateral wrist lesions showed an efficacy rate of 35 %. *Zu Shi Ma Xu Ji* [151] was prepared by soaking slices of *Zu Shi Ma* root in 1000 mL of 75 % alcohol and applied externally to patients with acute gouty arthritis. It was observed that pain was immediately reduced, and the patient was able to walk freely the following day.

5.2. Other Diseases

While *Zu Shi Ma* is a potent remedy for arthritis, advances in medical science have revealed its broader clinical applications. The injection of *Zu Shi Ma* [152] has demonstrated excellent efficacy in treating injuries in police dogs, with a rapid onset of therapeutic effects. Liu et al. [153] reported that after one course of treatment with *Zu Shi Ma Pian* combined with traditional Chinese medicine fumigation in 32 patients, the efficacy rate was 93.75 %, significantly higher than the 75 % efficacy

rate of oral non-steroidal anti-inflammatory drugs. Xing and Li [154] treated 40 patients with adhesive capsulitis using *Zu Shi Ma Pian* in combination with closed therapy. Post-treatment, clinical symptoms were effectively alleviated, and shoulder joint function showed significant improvement. The combination of *Zu Shi Ma Pian* [155] with extended-release ibuprofen capsules yields superior results in the treatment of acute episodes of low back pain. The relief spray *Zu Shi Ma Zhi Tong Pen Wu Ji* [156-157] effectively treats acute soft tissue injuries and is more effective than *Wu Song Zhong Tong Liniment*. Regional injection of *Zu Shi Ma Chang Xiao Zhi Tong Ji* [158] in postoperative anal surgery patients can relieve pain and reduce postoperative complications. Zhang et al. [159] treated 129 burn patients using *Zi Ni Su Xiao Shao Shang Ye*. All patients recovered spontaneously, with pain relief observed in 64 cases within 3 to 10 min of administration. The oral decoction of *Zu Shi Ma* and *Gan Cao* is effective in treating cardialgia and stomach pain [17].

5.3. Formulation Research

Owing to its low toxicity, *Zu Shi Ma* is primarily used externally, with the predominant marketed formulations being patches and ointments. Additionally, tablet, capsule, spray, and injection formulations, along with other dosage forms, are gradually being explored (see Table 5).

Zu Shi Ma Pian (Chinese Pharmacopoeia Standard Z20023018) is a traditional Chinese medicine primarily composed of *Zu Shi Ma* and has been included in the first part of the 2020 edition of the Pharmacopoeia of the People's Republic of China. It is effective not only in treating arthritis and rheumatoid arthritis but also in managing conditions such as sciatica and frozen shoulder caused by cold and damp obstruction of collaterals. Chen et al. [160] transformed *Zu Shi Ma Pian* into *Zu Shi Ma Jiao Nang* (Standard No: WS3-159(Z-53)-94(Z)) and employed high-performance liquid chromatography to quantify the primary component, daphnetin, thereby enabling more convenient and precise quality control of the formulation. Cheng et al. [161] utilized enteric-coated *Zu Shi Ma Chang Rong Zhi Ji* to treat arthritic mice, observing significant anti-inflammatory and analgesic effects. Additionally, the formulation significantly ameliorated pathological damage in the knee and ankle joints of adjuvant-induced arthritis rats. Furthermore, *Zu Shi Ma* can be decocted with *Gan Cao*, *Sheng Jiang*, and other herbs as an effective remedy for headaches and colds induced by wind-cold.

Currently, there are three main types of *Zu Shi Ma Gao Yao* available on the market: *Zu Shi Ma Gao Yao* (Department WS3-B-3456-98), *Zu Shi Ma Feng Shi Gao* (Regional Standard upgraded to National Standard WS-10810 (ZD-0810)-2002), and *Zu Shi Ma Guan Jie Zhi Tong Gao* (Department WS3-B-3456-98). The first two are traditional ointments, while the third is a modern adhesive plaster formulation with enhanced adhesive properties. *Fu Fang Zu Shi Ma Ruan Gao* [162] also demonstrates notable analgesic and anti-inflammatory effects. Additionally, Xia et al. [149] developed *Zu Shi Ma Xu Ji*, which achieved remarkable therapeutic effects in the treatment of acute gouty arthritis. Tinctures and ointments may induce more pronounced local reactions and are generally recommended for patients with more severe conditions. Patches are appropriate for the elderly, frail individuals, children, and women with lower back and leg pain.

The single-component *Zu Shi Ma* injection (Chinese Pharmacopoeia Standard Z14021014) exhibits properties of dispelling wind, removing dampness, promoting blood circulation, and relieving pain. This formulation is widely used in clinical practice. Sun [69] evaluated the preclinical safety of 15 batches of *Zu Shi Ma* injections and observed no allergic reactions or other adverse effects. Zhang

et al. [163] investigated the formulation process of *Huang Rui Xiang* injection to enhance quality control and ensure the safety and efficacy of the medication. Their research revealed that pH regulation during the formulation process is critical. If the conditions are alkaline, it may compromise the content of the primary component, Daphnetin (**114**), in the injection solution. The *Zu Shi Ma* injection [164] contains a complex array of chemical components, making pH control essential during its formulation.

Zhao et al. [165] developed the *Zu Shi Ma Zhi Tong Pen Wu Ji* relief spray and optimized the extraction process of *Zu Shi Ma* to maximize its therapeutic efficacy.

Table 5. Clinical application of *C. Daphnes*

Name of preparation	Formulation composition	Disease	Ref
Gui Ma Zhi Tong Gao	**Zu Shi Ma**, Dang Gui, Tie Bang Chui, Shan Lang Dang, Bo He Nao, Bing Pian, Zhang Nao, Shui Yang Suan Jia Zhi	Arthralgia, fall injury	[166]
Zi Ni Su Xiao Shao Shang Ye	Di Yu, Si Ji Qing Hong Yao Zi, Hong Hua, Pu Gong Ying, Niu Xi, **Zu Shi Ma**, Ku Shen, Dang Gui, San Qi, Bing Pian, Xue Jie	Burn and scald	[159]
Zu Shi Ma Shu Tong Tie	**Zu Shi Ma**, Xi Xin, Man Tuo Luo, Fang Feng, Cang Zhu, Qin Jiao	All kinds of pain caused by rheumatism	[167]
Zu Shi Ma Guan Jie Zhi Tong Gao	**Zu Shi Ma**, Zhang Nao, Bing Pian, Bo Henao, Shui Yang Suan Jia Zhi, Ben Hai La Ming, Er Jia Ben Che Xiang	All kinds of pain caused by rheumatism	[168]
Fu Fang Zu Shi Ma Ruan Gao	**Zu Shi Ma**, Shi Chang Pu, Zhi Cao Wu, Zhi Zi, Gan Cao	Arthritis	[162]
Fu Fang Zu Shi Ma Zu She ye	**Zu Shi Ma**, Qin Jiao, Qiao Huo, Du Huo	Arthritis	[164]

6. Adverse Effects and Toxicology

While *Zu Shi Ma* exhibits a range of pharmacological activities and is widely utilized in clinical practice for treating various types of joint and muscle pain, underscoring its significant therapeutic value, its potential toxicological risks should not be overlooked [169]. Although *Zu Shi Ma* is commonly formulated as topical preparations, its application can induce skin irritation, often manifested as papules and other adverse reactions. Experimental evidence suggests that this irritation is attributed to the presence of terpenoid compounds, such as daphnetoxin (**224**), in *Zu Shi Ma*, which contribute to skin irritation and numbness. The removal of this toxic component maintains therapeutic efficacy while reducing skin irritation [170]. Dou et al. [171] reported two cases of accidental ingestion of topical cannabis tincture, which resulted in poisoning.

The skin irritation and sensitization tests of *Zu Shi Ma Ning Jiao Gao* [172] revealed no erythema or edema on intact rabbit skin, indicating a lack of irritant effects. However, it exhibited mild irritant effects on damaged skin. The skin sensitization test in guinea pigs did not reveal significant allergic reactions, such as erythema or edema. Subcutaneous injections of *Zu Shi Ma Zhi Tong Pen Wu Ji* [173] in mice, administered once daily for seven consecutive days, did not affect the appearance, behavior, or mental status of the mice. No abnormal changes in body weight or visible organ lesions

were observed. The LD_{50} was 9.78–10.48 mL/kg. Concurrently, toxicity tests were conducted on rabbit skin by applying the test drug (1.4 mL) directly to the surface for 24 h, with continuous observation for 7 days. The central nervous system and limb activity of rabbits, regardless of skin condition, were unaffected. Additionally, the local skin color remained normal, and no irritant reactions were observed. Meanwhile, the acute dermal toxicity test of *Zu Shi Ma Shu Tong Tie* [167] on rats showed no signs of poisoning or mortality, with an LD_{50} greater than 5,000 mg/kg, indicating its actual non-toxicity. *Zu Shi Ma Ba Bu Ji* [174] exhibited no irritant effects on rabbit skin. Subsequently, it was tested on volunteers, with application to the skin for 24 h. The results indicated no occurrence of allergic reactions, such as redness, swelling, or other adverse effects.

Zou et al. [175] administered Daphnetin (**114**) to mice via oral gavage and monitored them continuously for 14 days. No signs of poisoning or mortality were observed, with an LD_{50} greater than 100 mg/kg body weight (bw). Additionally, mice were orally administered doses of 1.5, 3, and 6 g/kg bw and observed at 0 and 24 h. No inhibitory effects on bone marrow cells or genotoxicity were observed during this process.

In summary, the toxicological evaluation of various market formulations of *Zu Shi Ma* and its chemical components has demonstrated the absence of toxicity, genotoxicity, and irritant allergic reactions. These findings suggest that *Zu Shi Ma* maintains a high level of safety in its market applications, providing a solid foundation for further clinical development.

7. Conclusion and Prospect

This article reviews the research progress on the botany, phytochemistry, pharmacology, clinical applications, adverse reactions, and toxicology of *C. Daphnes*. To date, 284 compounds have been isolated and identified from *C. Daphnes*. Modern pharmacological studies have revealed its diverse therapeutic potentials, including anti-inflammatory, anti-tumor, antibacterial, immunomodulatory, antioxidant, and analgesic effects. Due to its traditional efficacy in dispelling wind, removing dampness, relieving pain, and dispersing stasis, *C. Daphnes* is primarily used in clinical practice to treat rheumatic conditions such as rheumatoid arthritis, wrist arthritis, and knee osteoarthritis. Additionally, with the ongoing advancement of modern technology, researchers have explored its applications in treating conditions such as canine sprains, shoulder periarthritis, lumbar pain, and burns.

It is important to note that while previous articles have reviewed the chemical composition and pharmacological effects of *C. Daphnes*, our review identifies a significant gap: there is no systematic and comprehensive summary encompassing the plant's description, distribution, chemical composition, pharmacological effects, clinical applications, preparation studies, and adverse reactions. This paper seeks to address these gaps by offering a comprehensive overview of the plant's chemical composition, pharmacological targets, and clinical applications.

Firstly, according to existing literature on the chemical constituents of *C. Daphnes*, a total of 284 compounds have been isolated. It is evident that 174, 118, and 53 compounds were identified from *D. giraldii*, *D. tangutica*, and *D. retusa*, respectively. Additionally, the majority of these compounds are predominantly concentrated in the root bark and stem bark, with only a small fraction being isolated from leaves and callus tissues.

Secondly, flavonoids constitute the primary chemical constituents of *C. Daphnes*, accounting for 37 % of the total isolated compounds. Additionally, coumarins are recognized as the primary

active ingredients. Notably, only one di-glycoside coumarin, daphnetin-8-O-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside (**116**), has been isolated from *C. Daphnes*. Therefore, further investigation is warranted to explore whether other parts of this plant harbor additional glycosidic coumarins. Moreover, rutin is considered a key active component, demonstrating significant pharmacological effects and serving as a crucial candidate for novel drug development. Furthermore, subsequent studies should aim to elucidate the reasons behind the differences in chemical compositions among various parts of *C. Daphnes*.

Thirdly, in the course of reviewing the literature, some scholars often confuse the origins of *C. Daphnes* due to regional discrepancies in standards. This confusion complicates efforts at accurate botanical classification. Therefore, further in-depth research is essential to clarify these issues. Additionally, due to overexploitation and slow growth cycles, wild populations of this plant are nearing extinction. The challenges associated with its cultivation have led to its classification as a nationally endangered species. Hence, it is recommended that future research extensively focus on the aerial parts of the plant to maximize the utilization of its medicinal components. Furthermore, research should aim to develop cultivation methods and controlled environments conducive to the rapid growth of this plant, thereby safeguarding it from extinction.

Fourthly, although *C. Daphnes* has broad applications in traditional folk medicine, its commercial availability remains limited to formulations like tablets, ointments, and injections, highlighting a lack of development in this area. Moreover, given the process of formulating ointments from *C. Daphnes*, concerns have been raised regarding the potential for high heavy metal content to cause skin irritation and possibly more severe damage. Therefore, it is recommended that future research focus on developing safer formulations, potentially incorporating hepatoprotective Chinese herbal medicines to mitigate potential harm while preserving efficacy. Additionally, comprehensive clinical studies are necessary to validate the efficacy and safety of *C. Daphnes*-based treatments for various diseases. Systematic documentation of the clinical applications of *C. Daphnes* would enable researchers to provide evidence-based recommendations for its integration into mainstream medical practice.

Fifthly, intensified efforts are required to elucidate the precise chemical structures of compounds found in *C. Daphnes* and to clarify their underlying mechanisms of action. This endeavor is crucial for fully harnessing the therapeutic potential of *C. Daphnes* and developing targeted drug interventions.

In conclusion, this review highlights the diverse therapeutic properties of *C. Daphnes* and underscores the critical need for comprehensive research to fully realize its potential. By addressing existing knowledge gaps and fostering international collaboration, *C. Daphnes* presents significant potential as a valuable natural resource for the development of novel therapeutic drugs and the advancement of global healthcare.

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