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Phytochemistry, Pharmacology, Toxicity and structure-activity of *Nerium oleander* L.: A Systematic Review

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Abstract: *Nerium oleander L.* is part of the Apocynaceae family and Nerium genus. Primarily found in subtropical areas, this plant is indigenous to the Mediterranean coast. It is also widely cultivated in China. To date, more than 146 compounds have been obtained from the plant, chiefly including cardiac glycosides, triterpenoids, phytosterols and other chemical constituents, of which cardiac glycosides are the main type of compounds with good pharmacological activity. Pharmacological studies have shown that *N. oleander* has anti-tumor, anti-diabetic, cardiotonic, hepatoprotective, anti-inflammatory, anti-viral, and other activities. This article provides important insights for future research, development, and use of this plant by summarizing the chemical contents, pharmacological properties, toxicity, and structure-activity connections of *N. oleander* over the previous 50 years.

Keywords: *Nerium oleander* L.; phytochemistry; pharmacology; cardiac glycosides; toxicity

1. Introduction

N. oleander is classified as the cardiac class of traditional Chinese medicine, bitter and cold in nature, toxic and belongs to the heart meridian, its effects are mainly cardiac

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diuretiexpectorant, asthma, analgesic, elimination of blood stasis [1]. *N. oleander* is mainly distributed in the Mediterranean and subtropical regions, originally from countries like India, Iran and Nepal. It has been introduced and widely cultivated in China. Furthermore, in addition to its medicinal value, it also possesses ornamental and environmental protection value due to its colorful corollas and leaves' ability to resist smoke and dust. In its place, the seeds of *N. oleander* can be pressed into lubricating oil. Meanwhile, the fiber strength of the stem bark was relatively good and could be used as a blended raw material [2].

Studies indicated that *N. oleander* contains cardiac glycosides, triterpenoids and flavonoids. Modern pharmacological studies showed that *N. oleander* had anti-tumor, anti-diabetic, cardiotonic, hepatoprotective, anti-inflammatory, anti-viral, and other activities. Based on preliminary experiments and a review of the literature, it was demonstrated through research that *N. oleander* also presented toxic effects.

This paper summarizes the latest research advancements regarding the chemical constituents, pharmacological activities, toxicity and structure-activity relationships of *N. oleander* in recent years, providing a reference for further research, development, and utilization of *N. oleander*.

2. Botany, Description and Distribution

Nerium oleander L., also known as the *Nerium indicum*, *Nerium odorum* or *Nerium oleander* var. indicum, was a type of evergreen upright large shrub classified under the Apocynaceae family and the *Nerium* genus. *N. oleander* has its origin in the Mediterranean region. Moreover, it is extensively grown across Europe, the Americas, and the tropical and subtropical regions of Asia. In China, the *N. oleander* was also extensively grown, including various cultivated varieties such as the *Nerium oleander* 'Paihua', *Nerium oleander* 'Variegatum', *Nerium oleander* 'Plenum', *Nerium oleander* 'Nanum' and *Nerium oleander* 'Roseum'.

The *N. oleander* is described in the "*Flora of China*" as an evergreen little tree or shrubby plant that may grow up to 6 m in height and has a watery sap. With a cuneate or decurrent base, an acuminate or acute apex, up to 120 pairs of parallel lateral veins, and a petiole that is 5~8 mm long, the leaves are leathery, narrowly elliptic-lanceolate, seldom opposite, and arranged in threes in a whorl. The cyme inflorescences are arranged in a corymbose, terminal manner. The fragrant flowers have 0.3~1 cm long calyx lobes that are either narrow triangular or narrow ovate. The corolla is fashioned like a funnel, with lobes that overlap to the right. It can be single or double, purple-red, pink, orange-red, yellow, or white, and it has a wide neck and a corolla tube that is 1.2~2.2 cm long. The corona lobes are five, petal-like and fringed. The stamens are fixed at the apex of the flower tube, with arrow-shaped anthers attached to the style, ear-shaped at the base and filamentous connective tissue covered with long soft hairs. There is no nectary disc. The ovary has two separate carpels. The fruit is a pair of independent, cylindrical follicles that measure 12~23 cm in length and 0.6~1 cm in diameter. The seeds are long, many, and have hairs that are 0.9~1.2 cm long. The plant flowers during spring, summer and autumn. The plant fruits from winter through spring [3].

Figure 1. Cultivars of *Nerium oleander* L.

3. Phytochemistry

N. oleander is rich in chemical components. Over the past decaderecent years, 146 compounds have been isolated from various sections of the *N. oleander*, including roots, leaves and branches. These compounds mainly included cardenolides (**1~80**), triterpenoids (**81~116**) and other chemical constituents (**117~146**). Among which, cardenolides were the most active components in *N. oleander*. The source, names and specific structures of compounds are shown in Table 1 and Figure 2 ~5.

Table 1. Constituents are isolated and identified from *Nerium oleander* L.

No.	Name	Plant	Part	Ref
Cardenolide				
1	Oleandrin	N1	Leaves	[4]
2	Odoroside A	N2	Stems and twigs	[5]
3	Odoroside B	N1	Dried aerial parts	[6]
4	Odoroside G	N1	Roots	[7]
5	Odorobioside G	N1	Roots	[7]
6	Neritaloside	N1	Stems and twigs	[8]
7	Nerigoside	N1	Leaves	[9]

8	Neridiginoside	N1	Leaves	[10]
9	16-*O*-acetylgitoxigenin	N1	Dried aerial parts	[6]
10	Deacetyloleandrin	N1	Dried aerial parts	[6]
11	Beaumontoside	N1	Leaves	[11]
12	Cardenolides N-1	N1	Stems and twigs	[12]
13	Cardenolides N-4	N1	Stems and twigs	[12]
14	*β*-anhydroepidigitoxigenin	N1	Roots	[13]
15	5*α*-oleandrigenin	N1	Roots	[7]
16	5*α*-oleandrigenin *β*-*D*-digitaloside	N1	Roots	[7]
17	16-*O*-acetylneogitostin	N1	Roots	[7]
18	3*β*-*O*-(*β*-*D*-diginosyl)-8,14*β*-dyhydroxy-5*β*,14*β*-card-16,20(22)-dienolide	N2	Stems and twigs	[5]
19	3*β*-*O*-(*β*-*D*-diginosyl)-14-hydroxy-5*β*,14*β*-card-16,20(22)-dienolide	N2	Stems and twigs	[5]
20	Odoroside H	N2	Stems and twigs	[5]
21	Oleandrigenin	N2	Stems and twigs	[5]
22	3*β*,14*β*-dyhydroxy-5*β*-card-20(22)-enolide	N2	Stems and twigs	[5]
23	3-hydroxy-5*β*-carda-8,14,20,(22)-trienolide	N1	Leaves	[9]
24	8-hydroxy-oleandrigenin-3-*O*-*β*-*D*-diginoside	N1	Dried aerial parts	[6]
25	3*β*-*O*-(*β*-*D*-diginosyl)-14*β*-hydroxy-5*β*,14*β*-card-8,16,20(22)-dienolide	N1	Dried aerial parts	[6]
26	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-diginopyranosyl]-16*β*-acetoxy-14-hydroxy-5*β*,14*β*-card-20(22)-enolide	N1	Leaves,roots, and root bark	[14]
27	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*α*-*L*-oleandropyranosyl]-16*β*-acetoxy-14-hydroxy-5*β*,14*β*-card-20(22)-enolide	N1	Leaves,roots, and root bark	[14]
28	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-sarmentopyranosyl]-16*β*-acetoxy-14-hydroxy-5*β*,14*β*-card-20(22)-enolide	N1	Leaves,roots, and root bark	[14]
29	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-digitalopyranosyl]-14-hydroxy-5*α*,14*β*-card-20(22)-enolized	N1	Leaves,roots, and root bark	[14]
30	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-diginopyranosyl]-16*β*-acetoxy-14-hydroxy-5*α*,14*β*-card-20(22)-enolide	N1	Leaves,roots, and root bark	[14]
31	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-digitalopyranosyl]-16*β*-acetoxy-14-hydroxy-5*α*,14*β*-card-20(22)-enolide	N1	leaves,roots, and root bark	[14]

32	3*β*-*O*-(*β*-*D*-glucosyl)-16*β*-acetoxy-14-hydroxy-5*β*,14*β*-card-20(22)-enolide	N1	Stems and twigs	[8]
33	3*β*-*O*-(*β*-*D*-digitalosyl)-14-hydroxy-5*α*,14*β*-card-20(22)-enolide	N1	Stems and twigs	[8]
34	3*β*-*O*-(*β*-*D*-sarmentosyl)-16*β*-acetoxy-14-hydroxy-5*β*,14*β*-card-20(22)-enolide	N1	Stems and twigs	[12]
35	3*β*-*O*-(*D*-digitalosyl)-21-hydroxy-5*β*-carda-8,14,16,20(22)-tetraenolide	N1	Roots	[13]
36	Digitoxigenin *β*-gentiotriosyl-(1→4)-*β*-*D*-digitaloside	N1	Roots	[7]
37	Uzarigenin *β*-gentiobiosyl-(1→4)-*β*-*D*-diginoside	N1	Roots	[7]
38	Oleandrigenin *β*-odorotriside	N1	Dried aerial parts	[15]
39	Oleandrigenin *α*-oleatrioside	N1	Dried aerial parts	[15]
40	Gitoxigenin *α*-oleatrioside	N1	Dried aerial parts	[15]
41	Δ^{16}- digitoxigenin *β*-neritrioside	N1	Dried aerial parts	[15]
42	Δ^{16}-digitoxigenin *β*-odorotrioside	N1	Dried aerial parts	[15]
43	Digitoxigenin *β*-neritrioside	N1	Dried aerial parts	[15]
44	Oleandriyenin *β*-neritrioside	N1	Dried aerial parts	[15]
45	Digitoxigenin *α*-oleatrioside	N1	Dried aerial parts	[15]
46	8*β*-Hydroxydigitoxigenin *β*neritrioside	N1	Dried aerial parts	[15]
47	Δ^{16}-8*β*-Hydroxydigitoxigenin *β*neritrioside	N1	Dried aerial parts	[15]
48	Cardenolides N-3	N1	Stems and twigs	[12]
49	Proceragenin	N1	Roots	[13]
50	Cardenolides B-2	N1	Stems and twigs	[8]
51	12*β*-hydroxy-5*β*-calane-8,14,16,20(22) -tetraenolactone	N1	Roots	[16]
52	Adynerin	N1	Leaves	[9]
53	5*α*-adynerin	N1	Dried aerial parts	[6]
54	Oleandigoside	N1	Leaves	[17]
55	Cardenolides B-1	N1	Stems and twigs	[8]
56	3*β*-*O*-(*β*-*D*-diginosyl)-8,14-epoxy-5*β*,14*β*-card-16,20(22)-dienolide	N2	Stems and twigs	[5]
57	3*β*-*O*-(*β*-*D*-digitalosyl)-8,14-epoxy-5*β*,14*β*-card-16,20(22)-dienolide	N2	Stems and twigs	[5]
58	8,14-epoxy-3*β*-hydroxy-5*β*,14*β*-card-20(22)-enolide	N1	Leaves	[9]
59	Δ^{16}-adynerigenin-*β*-*D*-sarmentosie	N1	Dried aerial parts	[6]
60	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-diginopyranosyl]-8,14-epoxy-5*β*,14*β*-card-20(22)-enolide	N1	Leaves,roots, and root bark	[14]

61	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-digitalopyranosyl]-8,14-epoxy-5*β*,14*β*-card-20(22)-enolide	N1	Leaves,roots, and root bark	[14]
62	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-digitalopyranosyl]-8,14-epoxy-5*β*,14*β*-card-16,20(22)-enolide	N1	Leaves,roots, and root bark	[14]
63	Adynerigenin *β*-neritrioside	N1	Dried aerial parts	[15]
64	Δ^{16}-adynerigenin *β*-neritrioside	N1	Dried aerial parts	[15]
65	Adynerigenin *β*-odorotrioside	N1	Dried aerial parts	[15]
66	Δ^{16}-adynerigenin *β*-odorotrioside	N1	Dried aerial parts	[15]
67	Δ^{16}-Adynerigenin *β*-gentiobiosyl-*β*-*D*-sarmentoside	N1	Dried aerial parts	[15]
68	Oleaside A	N2	Leaves	[18]
69	6*β*-hydroxyoleaside A	N1	Leaves	[18]
70	7*α*-hydroxyoleaside A	N2	Leaves	[18]
71	5*α*-oleaside A	N1	Dried aerial parts	[6]
72	16-Hydroxyoleaside A	N1	Dried aerial parts	[6]
73	Oleagenin	N1	Stems and twigs	[8]
74	Neriaside	N1	Leaves	[9]
75	14-carbonyl-neriaside	N1	Dried aerial parts	[6]
76	21-Hydroxy-neriaside	N1	Dried aerial parts	[6]
77	Neriagenin	N1	Dried aerial parts	[6]
78	3*β*-*O*-[*β*-*D*-glucopyranosyl-(1→4)-*β*-*D*-diginopyranosyl]-14*α*-hydroxy-8-oxo-8,14-sec-5*β*-card-20(22)-enolide	N1	Leaves,roots, and root bark	[14]
79	Neriagenin *β*-neritrioside	N1	Dried aerial parts	[15]
80	Δ^{16}-Neriogenin *β*-neritrioside	N1	Dried aerial parts	[15]
Triterpenoid				
81	Oleanolic acid	N2	Stems and twigs	[5]
82	1*β*,3*β*-Dihydroxyurs-12-en-28-oic acid	N1	Leaves	[19]
83	3*β*,13*β*-dihydroxyurs-11-en-28-oic acid	N1	Leaves	[20]
84	20*β*,28-epoxy-28*α*-methoxytaraxasteran-3*β*-ol	N1	Leaves	[21]
85	20*β*,28-epoxytaraxaster-21-en-3*β*-ol	N1	Leaves	[21]
86	Oleanderolide	N1	Leaves	[20]
87	Oleanderic acid	N1	Leaves	[21]
88	Kanerocin	N1	Leaves	[22]
89	3*α*-acetoxy-urs-18,20-dien-28-oic acid	N1	Leaves	[22]
90	Uncarinic acid A	N1	Dried aerial parts	[6]
91	Myricerol	N1	Dried aerial parts	[6]
92	28-Hydroxylup-20(29)-ene-3,7-dione	N1	Leaves	[22]
93	Oleanderocioic acid	N1	Leaves	[17]

94	Lupa-12,20(29)-diene-3*β*,27,28-triol	N1	Leaves	[23]
95	Lupeol	N1	Leaves	[4]
96	Betulinic acid	N1	Dried aerial parts	[6]
97	Betulin	N1	Leaves	[20]
98	(20*S*,24*S*)-Epoxydammarane-3*β*,25-diol	N1	Leaves	[20]
99	(20*S*,24*R*)-epoxydammarane-3*β*,25-diol	N1	Leaves	[20]
100	28-norurs-12-ene-3*β*,17*β*-diol	N1	Leaves	[21]
101	3*β*-hydroxyurs-12-en-28-aldehyd	N1	Leaves	[21]
102	Ursolic acid	N1	Leaves	[20]
103	3*β*,27-dihydroxy-12-ursen-28-oic acid	N1	Leaves	[20]
104	3*β*-hydroxyurs-12-en-28-aldehyde	N1	Leaves	[20]
105	28-norurs-12-en-3*β*-ol	N1	Leaves	[20]
106	Urs-12-en-3*β*-ol	N1	Leaves	[20]
107	Urs-12-ene-3*β*,28-diol	N1	Leaves	[20]
108	Uncarinic acid C	N1	Dried aerial parts	[6]
109	Ursolic aldehyde	N1	Dried aerial parts	[6]
110	Neriucoumaric acid	N1	Leaves	[24]
111	Isoneriucoumaric acids	N1	Leaves	[24]
112	Oleanderolic acid	N1	Leaves	[22]
113	*α*-Neriursate	N1	Leaves	[25]
114	*β*-Neriursate	N1	Leaves	[17]
115	Trans-karenin	N1	Leaves	[26]
116	Cis-karenin	N1	Leaves	[26]
Others				
117	Neristigmol	N1	Leaves	[17]
118	*β*-sitosterol	N2	Stems and twigs	[5]
119	*β*-sitosterol-3-*O*-*β*-*D*-glucopyranosid	N2	Stems and twigs	[5]
120	5*α*-pregnnnolone bis-*O*-*β*-*D*-glucosyl-(1→2,1→6)-*β*-*D*-glucoside	N1	Roots	[7]
121	Pregneaolone *β*-*D*-apiosyl-(1→6)-*β*-*D*-glucoside	N1	Roots	[7]
122	*β*-gentiobioside	N1	Roots	[7]
123	Pregnenolone bis-*O*-*β*-*D*-glucosyl-(1→2,1→6)-*β*-*D*-glucoside	N1	Roots	[7]
124	Neridhone-B	N1	Leaves	[9]
125	12*β*-hydroxypregna-4,6-diene-3,20-dione	N1	Dried aerial parts	[6]
126	20-*R*-hydroxypregna-4,6-diene-3,20-dione	N1	Dried aerial parts	[6]
127	Neridienone A	N1	Roots	[13]
128	(20S)-20,21-Dihydroxypregna-4,6-diene-3,12-dione	N1	Bark and twigs	[27]

129	21-Hydroxypregna-4,6-diene-3,12,20-trione	N1	Bark and twigs	[27]
130	12*β*-Hydroxypregn-4-ene-3,20-dione	N1	Root bark	[28]
131	12*β*-Hydroxy-16*α*-methoxypregna-4,6-diene-3,20-dione	N1	Root bark	[28]
132	14,16-dihydroxy-3-oxo-y-lactone-pren-4-en-21-oic acid	N1	Leaves	[9]
133	16,17-epoxy-12-hydroxy-progesterone-4,6-dienolide-3, 20-diketone	N1	Leaves	[9]
134	Quercetin-3-*O*-robibioside	N1	Leaves	[4]
135	Rutin	N1	Leaves	[4]
136	Luteolin-5-*O*-rutinoside	N1	Flowers	[27]
137	Luteolin-7-*O*-rutinoside	N1	Flowers	[27]
138	Kaempferol-5-*O*-*α*-*L*-rhamnopyranosyl-(1→6)-*β*-*D*-glucopyranoside	N1	Leaves	[17]
139	8*α*-methoxylabdan-18-oic acid	N1	Leaves	[23]
140	12-ursene	N1	Leaves	[23]
141	Scopolide	N2	Stems and twigs	[5]
142	P-hydroxyacetophenone	N2	Stems and twigs	[5]
143	Neriumol	N1	Leaves	[24]
144	Nerifol	N1	Leaves	[24]
145	Trans-5-*O*-caffeoylquinic acid	N1	Flowers	[29]
146	Pheophytin A	N2	Stems and twigs	[5]

N1: *Nerium oleander* L.; N2: *Neriumindicum mill.cv* Paihua

3.1. Cardiac Glycosides

In total, 80 cardenolide compounds (**1~80**) have been isolated from *Nerium oleander* L. These unique components are widely distributed throughout the roots, stems, leaves, and other plant parts. Type A and Type B cardenolide aglycones are distinguished by the type of unsaturated lactone ring present at the C_{17}-position. At present, the aglycones of cardiac glycosides isolated from *N. oleander* are all Type A cardiac glycosides. And it had been found that their aglycones are all Type A cardenolides, mainly consisting of digitoxigenin, oleandrigenin, and uzarigenin, which are composed of 23 carbon atoms. Among them, uzarigenin has a trans configuration for the A/B ring fusion, while the others are cis. The C/D rings in the cardenolide aglycones are all cis. The C_3 and C_{14}-positions on the cardenolide aglycone nucleus are both in the *β* configuration. And the C_3-position is connected to sugar [30]. The C_5-position of uzarigenin was in the *α*-configuration, while the C_{16}-position of oleandrigenin was an acetoxy group. Cardenolide compounds are the main active components of *N. oleander*. Such as Oleandrin (**1**) has antitumor, antiviral, and anti-inflammatory pharmacological effects. The specific compound names, sources and structures can be seen in Table 1~2 and Figure 2~3.

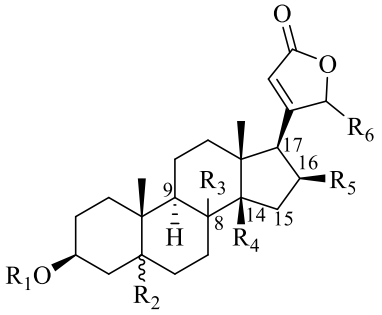
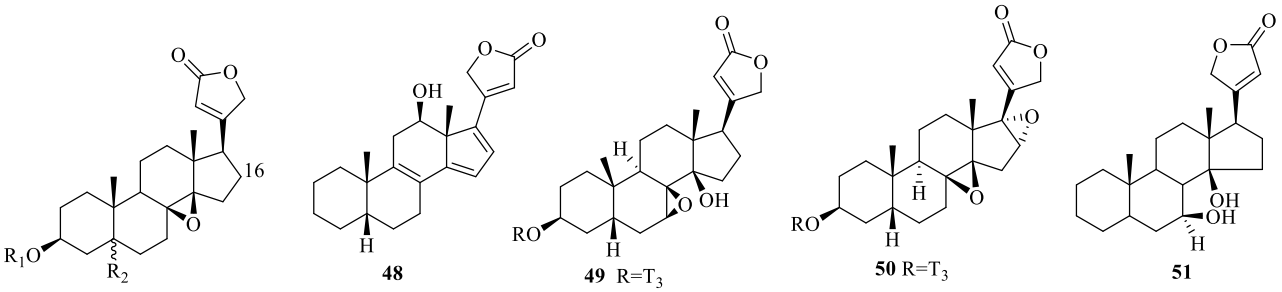


Figure 2. Parent nuclei of compounds **1~47**

Table 2. Structures of compounds **1~47**

Compound	R_1	R_2	R_3	R_4	R_5	R_6	
1	T_1	β-H	H	OH	OAc	H	
2	T_3	β-H	H	OH	H	H	
3	T_3	α-H	H	OH	H	H	
4	T_{13}	β-H	H	OH	H	H	
5	T_7	β-H	H	OH	H	H	
6	T_4	β-H	H	OH	OAc	H	
7	T_3	β-H	H	OH	OAc	H	
8	T_3	OH	H	OH	H	H	
9	T_8	β-H	H	OH	OAc	H	
10	T_3	β-H	H	OH	OH	H	
11	T_1	β-H	H	OH	OH	H	
12	T_2	β-H	H	OH	OH	H	
13	T_3	α-H	H	OH	OAc	H	
14	T_8	α-H	H	H	H	H	$\Delta^{14,15}$
15	T_2	α-H	H	OH	OAc	H	
16	T_4	α-H	H	OH	OAc	H	
17	T_{20}	β-H	H	H	OAc	H	
18	T_3	β-H	OH	OH	H	H	
19	T_3	β-H	H	OH	H	H	$\Delta^{16,17}$
20	T_4	β-H	H	OH	H	H	

21	T_8	β-H	H	OH	OAc	H	
22	T_8	β-H	H	OH	H	H	
23	T_8	β-H	H	H	H	H	$\Delta^{8,9}\Delta^{14,15}$
24	T_3	β-H	OH	OH	OAc	H	
25	T_3	β-H	H	OH	H	H	$\Delta^{8,9}\Delta^{16,17}$
26	T_5	β-H	H	OH	OAc	H	
27	T_6	β-H	H	OH	OAc	H	
28	T_9	β-H	H	OH	OAc	H	
29	T_7	α-H	H	OH	H	H	
30	T_5	α-H	H	OH	OAc	H	
31	T_7	α-H	H	OH	OAc	H	
32	T_4	β-H	H	OH	OAc	H	
33	Glc	β-H	H	OH	OAc	H	
34	T_2	β-H	H	OH	OAc	H	
35	T_4	β-H	H	H	H	OH	$\Delta^{8,9}\Delta^{14,15}$ $\Delta^{16,17}$
36	T_{12}	β-H	H	OH	H	H	
37	T_{13}	α-H	H	OH	H	H	
38	T_{13}	β-H	H	OH	OAc	H	
39	T_{17}	β-H	H	OH	OAc	H	
40	T_{14}	β-H	H	OH	OH	H	
41	T_{15}	β-H	H	OH	H	H	$\Delta^{16,17}$
42	T_{16}	β-H	H	OH	H	H	$\Delta^{16,17}$
43	T_{15}	β-H	H	OH	H	H	
44	T_{15}	β-H	H	OH	OAc	H	
45	T_{14}	β-H	H	OH	H	H	
46	T_{15}	β-H	OH	OH	H	H	
47	T_{15}	β-H	OH	OH	H	H	$\Delta^{16,17}$



	R_1	R_2	
52	T_3	β-H	
53	T_3	α-H	
54	T_8	β-H	$\Delta^{16,17}$
55	T_4	β-H	
56	T_3	β-H	$\Delta^{16,17}$
57	T_4	β-H	$\Delta^{16,17}$
58	T_8	β-H	
59	T_2	β-H	$\Delta^{16,17}$
60	T_5	β-H	
61	T_7	β-H	
62	T_7	β-H	$\Delta^{16,17}$
63	T_{12}	β-H	
64	T_{15}	β-H	$\Delta^{16,17}$
65	T_{16}	β-H	
66	T_{16}	β-H	$\Delta^{16,17}$
67	T_{17}	β-H	$\Delta^{16,17}$

	R_1	R_2	R_3	R_4	R_5
68	T_3	β-H	H	H	H
69	T_3	β-H	OH	H	H
70	T_3	β-H	H	OH	H
71	T_3	α-H	H	H	H
72	T_3	β-H	H	H	OH
73	H	β-H	H	H	H

	R_1	R_2	R_3	R_4	
74	T_3	β-H	αH	H	
75	T_3	α-H	=O	H	
76	T_3	β-H	αOH	OH	
77	T_3	β-H	αOH	H	
78	T_5	β-H	αOH	H	
79	T_{15}	β-H	αOH	H	
80	T_{15}	β-H	αOH	H	$\Delta^{16,17}$

Figure 3. Structure of compounds **48**~**80**

3.2. Triterpenoids

At present, 36 triterpenoid compounds (**81~116**) have been isolated from *N. oleander*. The majority of these are pentacyclic triterpenoids, including oleanane-type, ursane-type and lupine-type compounds. Ming Zhao et al isolated two novel taraxasterane-type triterpenoids, designated as compounds **84** and **85**, from methanol extract of *N. oleander* [21]. For detailed compound names, sources, and structures, refer to Table 1 and Figure 4.

3.3 Others

In addition, three phytosterols (**117-119**), fourteen pregnanes (**120-133**), five flavonoids (**134-138**), two terpenoids (**139-140**) and other types (**141-146**) have been isolated from *N. oleander*. Furthermore, Siham Ayouaz and colleagues utilized microwave-assisted extraction (MAE) for the isolation of phenolic compounds from the leaves of *N. oleander* [31]. For the specific names, sources, and structures of these compounds, refer to Table 1 and Figure 5.

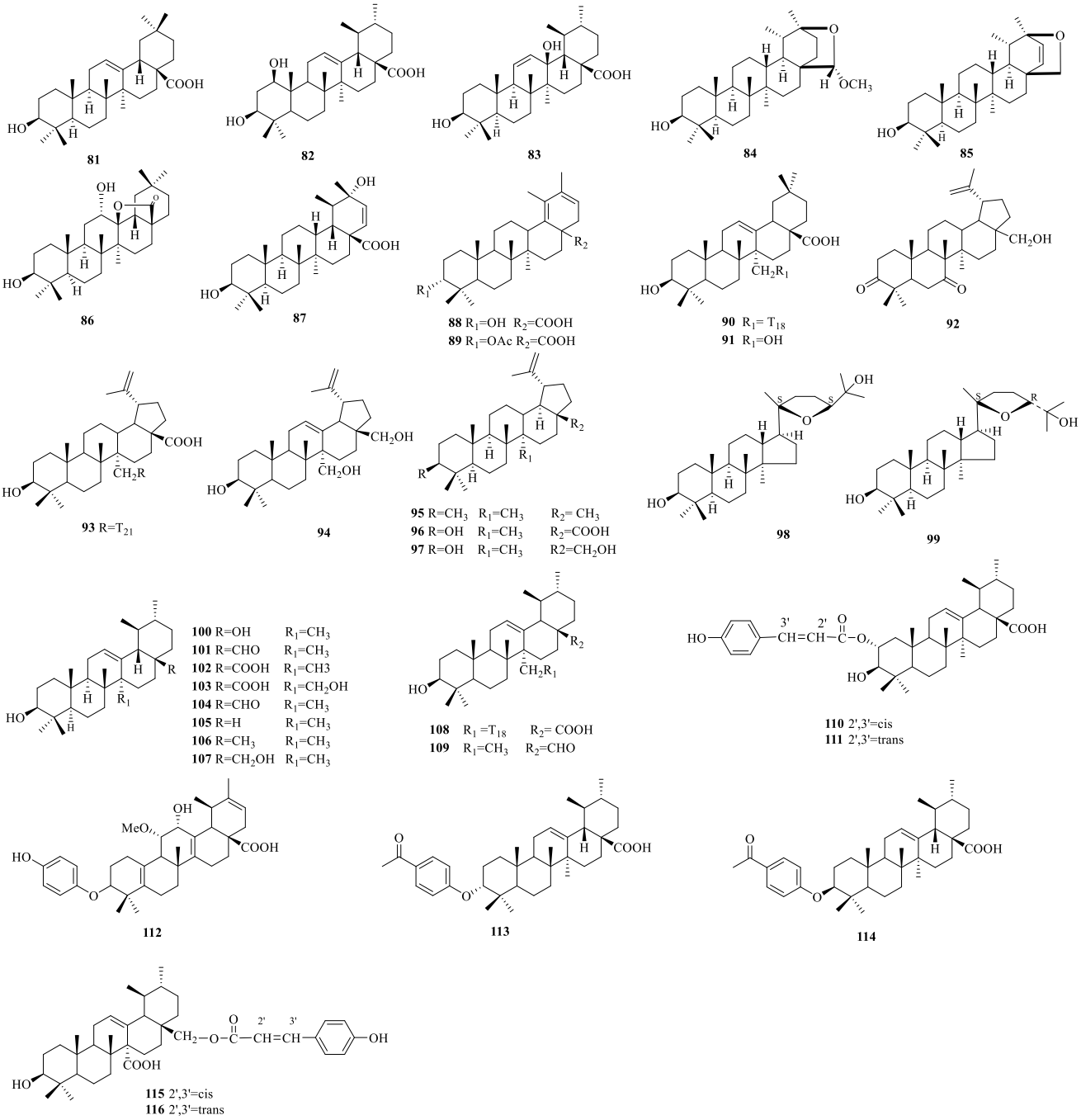


Figure 4. Structure of compounds **81~116**

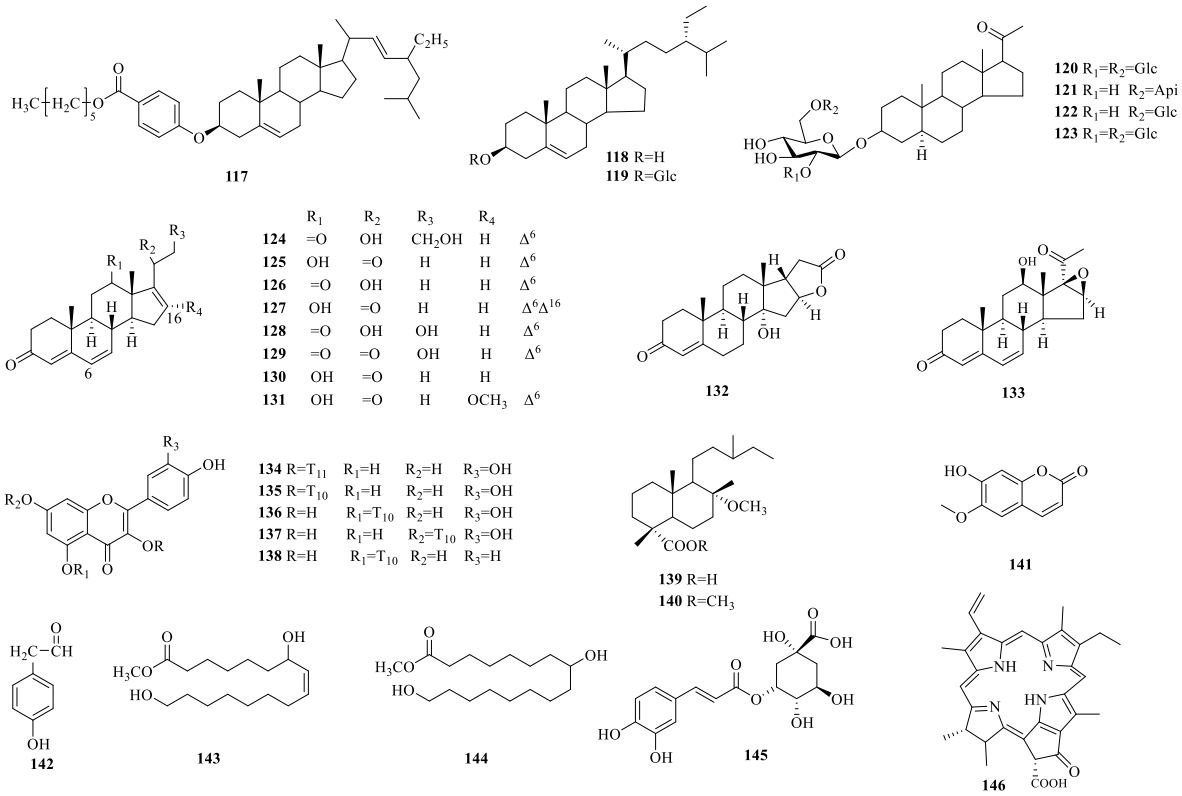


Figure 5. Structure of compounds **117~146**

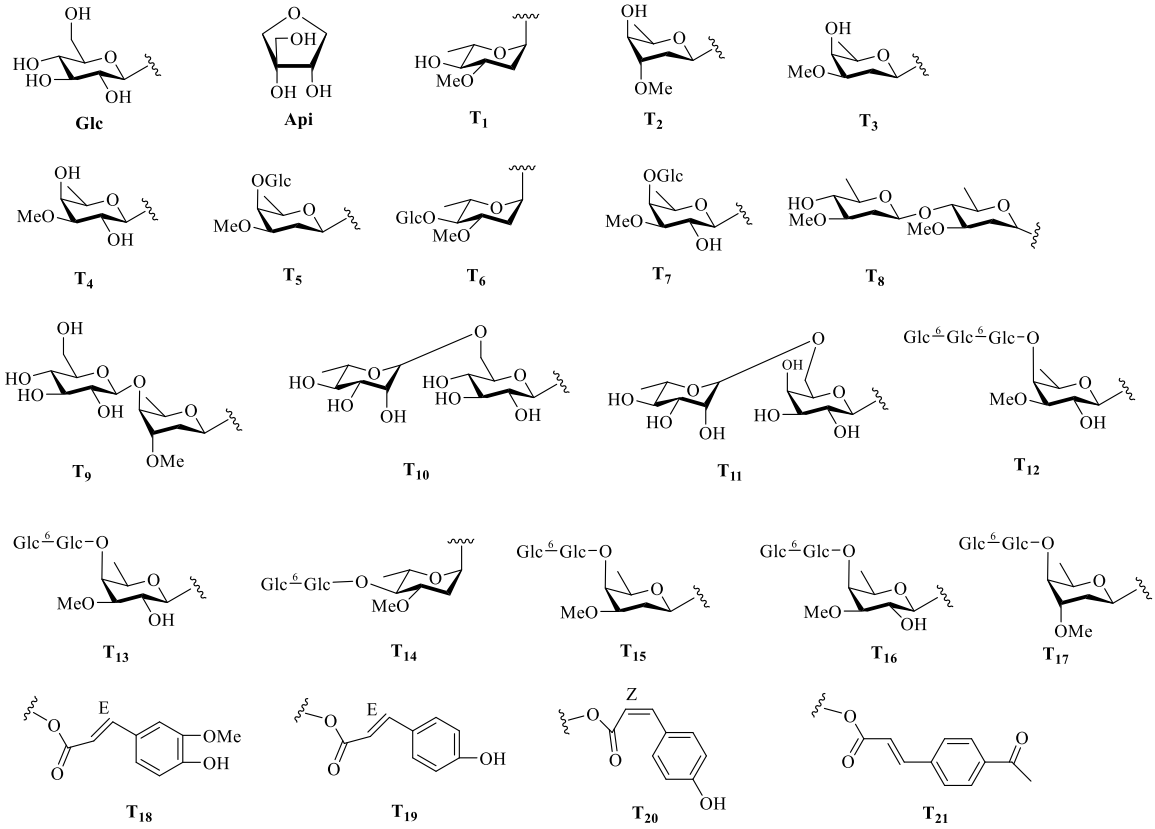


Figure 6. The structure of the substituents is described in the paper

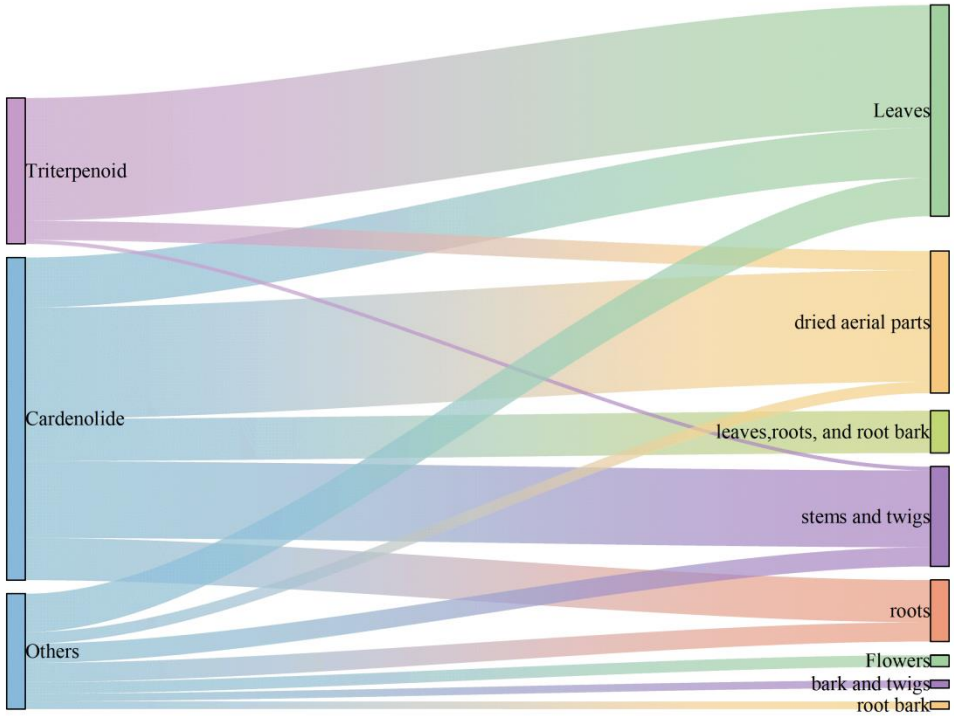


Figure 7. Distribution of compounds in *Nerium oleander* L.

4. Pharmacological Activity

Nerium oleander L. has been shown in recent studies to possess a number of pharmacological actions, including antitumor, antidiabetic, cardiotonic, hepatoprotective, anti-inflammatory, antiviral, and other properties. Information on the pharmacological activities of *Nerium oleander* L. is presented in Table 3.

4.1. Antitumor Activity

The extracts and cardiac glycosides from *N. oleander* have good antitumor activity. Modern research showed that oleandrin (**1**) has the strongest antitumor in *N. oleander* which could effectively inhibit the growth of cancer cells [32]. Studies have shown that oleandrin exerts its antitumor effect by inducing cell apoptosis and triggering rapid DNA damage response, which leads to cell death [33]. The anti - cancer mechanism of it lies in the suppression of the activation of nuclear transcription factor-κB (NF-κB) and activator protein -1 (AP-1), along with the promotion of apoptosis. Oleandrin exerts a substantial inhibitory impact on the proliferation of cells in the human pancreatic cancer cell line PANC - 1 by suppressing pAKT and up-regulating pERK [34]. Eroğlu Güneş et al. found that oleandrin affects TLR- associated genes and miRNA in A375 melanoma-derived cells. The experiments showed that *N. oleander* significantly inhibited the expression of IRAK1, MyD88, IRAK4, TRAF3 and TLR2-TLR7 [35]. Additionally, the TLRs pathway, hsa-miR-21-5p and hsa-miR-146a-5p were also discovered to be potentially implicated in the molecular basis of oleandrin's action. Oleandrin was also capable of killing

various breast carcinoma cell lines, inducing immunogenic cellular demise in breast tumor cells and activating antitumor immune responses both in vitro and in vivo. It induced immunogenic apoptosis in breast cancer cells through ER stress, thereby activating the mitochondrial apoptosis pathway to induce apoptosis [36]. Ko et al. assessed the anti-tumor capabilities of odoroside A (2) and oleandrin against human breast cancer cells that possess high metastatic tendency and are resistant to radiotherapy. That reduced the levels of *β*-catenin protein and octamer-binding transcription factors 3/4 (OCT3/4), along with the activity of matrix metalloproteinase-9 (MMP-9). The findings suggest that the anti - tumor mechanisms of oleandrin and odoroside A might entail the inhibition of invasion via the phospho-STAT-3 mediated pathway [37]. In addition, oleandrin could prevent migration, growth, and incursion of hepatocellular carcinoma cells (HepG2) while preventing skin cancer treatment [38,39]. The primary active ingredient of the anticancer candidate drug PBI-05204 was oleandrin. Hong et al. firstly investigated PBI-05204's pharmacokinetic characteristics, pharmacodynamic effects, and security in patients with advanced cancer. Evaluation of dose-dependent adverse effects in patients revealed that AKT and pS6 phosphorylation levels were reduced by 10 % and 35 % in pre-treatment and post-treatment peripheral blood mononuclear cell (PBMC) samples, respectively. This indicated that PBI-05204 has good survivability in sick people with advanced cancer and the proposed Phase II dosing was 0.2255 mg/kg/day [40]. Since then, this botanical drug has been examined in Phase I and Phase II clinical test. In the future clinical test for this complex scenario of cancer treatment, the efficacy of combining it with chemotherapy and radiotherapy as standard treatment will be probed [41].

In the *N. oleander*, other compounds have antitumor activity. The proliferative ability of colon cancer cells was inhibited by Odoroside A and Nerigoside (**7**). Nerigoside hindered the progression of colorectal cancer cells. This was achieved by obstructing the ERK/GSK 3*β*/*β* - catenin signaling transduction pathway [42,43]. 5α-oleandrin could inhibit Wnt-targeted genes in osteosarcoma cells. Treating fourth-generation KF cells with mitomycin-C, 5α-oleandrin and diluted medium, it was found that the proliferation index, collagen deposition index and migration ability were reduced. The results showed that 5α-oleandrin exerts a favorable anti-fibrotic influence on the activity of keloid fibroblasts [44].

Hydro-alcoholic extracts from diverset parts of the *N. oleander* also possessed anti-titumor activity. Ethanol extracts from the leaves, stems, and roots of *N. oleander* have shown cytotoxic activity on leukemia cells (HL60/K562). It was found that each extract at doses of 1000, 500 and 50 μg/mL all had significant anti-leukemia effects, and the inhibition of the P-gp pump in leukemia cell lines by oleander extract contributed to its cytotoxic effect [45]. Additionally, Pollen extracts derived from *N. oleander* inhibited the proliferation of colorectal cancer cell lines, yet they did not exhibit any cytotoxic effects on intact Caco-2 cells [46].

4.2 Antidiabetic Activity

Extracts from the *N. oleander* showed promising effects in the treatment of diabetes. *N. oleander* extracts demonstrated a notable anti-hyperglycemic effect in streptozotocin-induced diabetic mice, as evidenced by a 73.39% attenuation of blood glucose following 20 days of treatment. The study demonstrated that *N. oleander* possesses certain activity in the therapy of diabetes [47]. *N. oleander* flowers, roots, and stem extracts all showed efficacy in lowering blood glucose levels. Priyankar et al. examined the use of *N. oleander* stem and roots extracts to raise serum insulin levels in hyperglycemic rats. Through research using HPLC and molecular docking

indicated that the elevation of systemic antioxidant status mediated by *N. oleander* might be associated with the improvement of blood glucose levels [48]. Battal and colleagues conducted an in - depth investigation into the impacts of the ethanolic extract derived from the flowers of *N. oleander* (NFE) on streptozotocin (STZ) -induced diabetic rats. The analysis demonstrated that NFE could reduce glycated hemoglobin (HbA1c) and blood glucose levels, increase C-peptide and insulin hormone levels. It was also found that NFE had anti-immunotoxins and anti-neurotoxins effects on the liver tissue of diabetic rats [49]. Furthermore, the distillate of oleander has also been shown to have therapeutic effects on diabetes. Ayaz et al. researched the therapeutic effects of *N. oleander* in diabetic cardiomyopathy, treating it with distilled *N. oleander*, which eliminated the amplitude reduction and kinetic changes caused by diabetes. The results indicated that the distillate of *N. oleander* was a promising drug in the treatment or prevention of excitation-contraction coupling in diabetes [50]. Additional investigation revealed that *N. oleander* distillate could lower low-density lipoprotein, total cholesterol, and fasting glucose. Moreover, the *N. oleander* -10 distillation liquid might enhance the expression of PPAR-α - γ mRNA in the liver as well as PPAR - α, β, and γ mRNA within the adipose cellular environment. This presents a new therapeutic alternative for Type 2 diabetes mellitus (T2DM) [51].

4.3. Cardiotonic Activity

The extracts derived from *N. oleander* exerted a cardiotonic action, capable of boosting the contractility of the heart muscle. The research found that the ethanol extract of *N. oleander* had a cardiotonic effect on the isolated guinea-pig heart. Its effect on cardiac contractility showed a dose-dependent increase, which was similar to the effect of digoxin [52].Moreover, the powder of dried *Nerium oleander* leaves also enhanced the contractility of frog hearts [53]. Gayathri et al. discovered that therapy with ethanolic water extract of *N. oleander* flowers and propranolol produced an effect in rats with isoproterenol induced myocardial toxicity. This treatment prevented depletion of key antioxidant components, maintaining enzymatic (SOD, GSH-Px) and non-enzymatic (GSH, nitrite) systems. Therefore, it reduced lipid peroxidation. It has been ascertained that the aqueous alcohol extract of *N. oleander* flowers could improve the antioxidant defense system in the stage of experimental myocardial necrosis, which has a certain cardioprotective effect [54].

4.4. Hepatoprotective Activity

N. oleander is mentioned in both Indian and traditional Chinese medicine for its hepatoprotective effects. It was found that the hydro-alcoholic extracts derived from the roots, stems and leaves of *N. oleander* had a strong hepatoprotective effect on mice with halogenated alkane-induced liver injury [55]. Additional investigation showed that *N. oleander* may shield HepG2 cells from oxidative damage caused by LPS and that this hepatoprotective action is mediated by a mechanism that is independent of Toll-like receptor 4 (TLR4) [6]. Besides, the hydroethanolic extracts derived from the stem and root of *N. oleander* also exhibit hepatoprotective properties in mice intoxicated with carbon tetrachloride. Both in vitro and vivo research confirmed that the extract enhanced hepatic catalase activity, decreased lipid peroxidation, and reduced pro-inflammatory TNF-*α* levels [57].

4.5. Antiinflammatory Activity

The hydro-alcoholic extract of *N. oleander* leaves (NLLF) exhibits potent immunomodulatory activity in vitro. It was capable of upregulating the level of IFN-γ, IL-2 and IL-10, downregulating the level of TNF-α and IL-4 and stimulating the level of immunoglobulin levels in mice. By modulating immune activity, it could subsequently impact the therapy of inflammatory illnesses [58]. Shafiq et al. researched the antiinflammatory effects of the ethanolic extract of *N. oleander* flowers (NOEE). It was found that NOEE could reduce the levels of NO, tumor necrosis factor-α, prostaglandin E2 and interleukin-1β proteins, inhibit the expression of inducible tumor necrosis factor-α, nitric oxide synthase, interleukin-1β and cyclooxygenase-2 (COX-2) mRNA and significantly reduce the total white blood cells and C-reactive protein levels [59]. Furthermore, oleandrin (**1**) which was extracted from *N. oleander*, demonstrated anti-inflammatory properties by preventing NF-κB and AP-1 from activating [60], On the other hand, odoroside A (**2**) was able to suppress the amount of ICAM-1 that inflammatory cytokines elicited and prevent NF-κB-induced protein expression by blocking Ne+ dependent amino acid transporter activity [61].

4.6. Antiviral Activity

Extracts and compounds from *N. oleander* exhibited inhibitory effects on viruses such as Human Immunodeficiency Virus type 1 (HIV-1), Human T-cell leukemia virus type 1 (HTLV-1) and Poliovirus type 1. Shailbala Singh et al. explored the therapeutic effectiveness of the water-based extract of *N. oleander* (Anvirzel™) in combating HIV-1. The findings indicated that Anvirzel™ markedly decreased the expression level of the envelope glycoprotein gp120. Subsequently, *N. oleander* extract or oleandrin inhibited the formation of viral synapses, spreaded of HTLV-1 in vitro,which possessed a wide range of antiviral activity [62]. Hutchison T et al. demonstrated that a certain approach could combat enveloped viruses by reducing the binding of envelope glycoproteins to mature virions [63]. Moreover, at a concentration of 0.1 μg/ml, oleandrin decreased the generation of the infectious virus SARS-CoV-2 by more than 3000-fold [64]. Research showed that both cold and hot extracts of *N. oleander* had inhibitory effects on Poliovirus type 1 (PV1). Further evidence suggested that *N. oleander* exerted inhibitory effects in the first 2 hours after the infection period [65].

4.7. Other activities

The stems and leaves extract of *N. oleander* also showed antimicrobial activity. They exhibit effectiveness for all kinds of bacteria, such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Xanthomonas campestris*, and *Fusarium triticum* [66,67]. The study also demonstrated that *N. oleander* leaf extracts could serve as both reducing and stabilizing agents for the biosynthesis of cost-effective and biocompatible silver nanoparticles (AgNPs). The resulting AgNP-incorporated nanofibers exhibited potent antimicrobial activity against pathogenic microorganisms commonly found in human wounds [68]. Examination of the pollen extract from *N. oleander* revealed the presence of phenolic acids and flavonoid derivatives that possess antioxidant activity. Furthermore, polysaccharides extracted from *N. oleander* flowers demonstrated the ability to inhibit beta-amyloid (Aβ) peptide-induced phosphorylation of c-Jun N-terminal kinase (JNK-1), suggesting neuroprotective benefits in Alzheimer's disease [69].

5. Toxicity

Although *N. oleander* is widely utilized for treating various illnesses, the extracts and certain chemical components of it might be toxic. During the clinical application process, we found that it remains in certain organs of the human body, which may cause toxic reactions. *N. oleander* poisoning is mainly manifested in cardiotoxicity, and it can also damage other organs, for instance the heart, liver and lungs.

It was indicated that patients developed symptoms of poisoning, such as thrombocytopenia, approximately 72 h after ingesting *N. oleander* [78]. Botelho et al. conducted both in vivo and vitro tests and discovered that the aqueous-alcohol (1:1) extract of *N. oleander* may kill Cavia porcellus and induce severe arrhythmia. They determined that intracellular Na^+ buildup was caused by blockage of the Na^+/K^+-ATPase pump, which was the mechanism of toxicity [79]. According to additional research, mice's mean red blood cell volume, platelet count, TNF-α and interleukins (IL-1 and IL-6) were all markedly elevated by a 90% ethanol extract of *N. oleander* leaves. This finding implies that the extract exerts detrimental impacts on both cardiac and hepatic functions [80-81]. Additionally, *N. oleander* extracts also exhibited neurotoxicity. Biochemical and pathological analysis in mice and rats showed that *N. oleander* could effect serum CK and troponin levels after nerve damage and rats are more sensitive to the toxic effects of *N. oleander* [82].

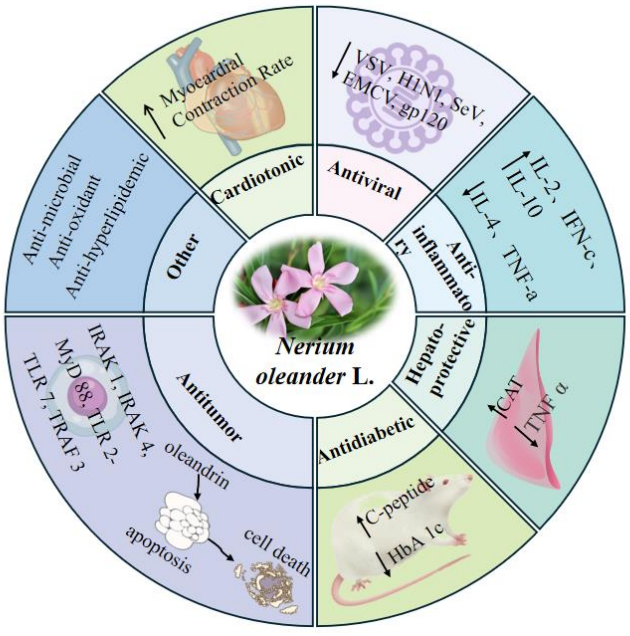


Figure 8. A brief summary of the pharmacological effects of *Nerium oleander* L

In further research on the mechanism of *N. oleander* toxicity, Ruta LL et al. used a *Saccharomyces cerevisiae* model to elucidate the toxicity of oleandrin (**1**). They discovered that exposure to aequorin triggered an influx of Ca^{2+} into the cytoplasm. It was found that exposure to aequorin in jellyfish could cause Ca^{2+} to flow into the cytoplasm without pumping Ca^{2+} from the cytoplasm into the vacuole, thereby increasing the toxicity of *N. oleander* [83]. Ethanolic extracts of *N. oleander* and saponin components are also toxic to zebrafish and crucian carp, which may affect the growth metabolism of juvenile fish [84-85].

Table 3 The pharmacological activities, extract, dose, model and results of *Nerium oleander L*. are summarized.

Pharmacological activities	Compounds/Extracts	Animal/Cell lines/virus	Model/Diseases	Result/Mechanism	Dosage	Plant	References
Anti-tumor activity	oleandrin	A375 cell line/in vitro	A375 human melanoma cell line	↓ IRAK1, IRAK4, MyD88, TLR2-TLR7, TLR4, TRAF3	/	N1	[35]
	oleandrin	A549 cells and ATDC5 cells/in vitro	A549 and ATDC5 cells treated with oleandrin	RAD51 inhibition led to XRCC up - regulation.	0.01,0.02,0.04μg/mL	N1	[33]
	leaf, stem and root extracts of *Nerium oleander*	K562 and HL60 cells/in vitro	*Nerium oleander* extract-treated K562 and HL60 cells	↓ P-gp	1000,500,50μg/mL	N1	[45]
	oleandrin and odoroside A	MDA-MB-231 breast cancer cells/in vitro	oleandrin and odoroside treated MDA-MB-231 cancer cells	STAT3 pathway suppresses invasion	50nm and100nm	N1	[70]
	odoroside A	HT29, SW620, HCT116, et al. cells lines/in vitro	odoroside A treated HT29, SW620, HCT116 cells lines	Inhibit CRC cells and induce apoptosis	(0, 100, 200, 400, 800 nM) for 14 days	N1	[42]

extraction of phenolic compounds from *Nerium oleander* leaves	Caco-2 and HT29 cell lines/in vitro	*Nerium oleander* leaves extract treated Caco-2 and HT29 cell lines	Inhibit HT29 colorectal cancer cell growth	Caco-2 cells(62.5μg/mL)	N1	[31]
Oleandrin	mice/in vivo	Tpa induced CD-1 mouse skin tumor model	TPA-induced PI3K/Akt/NF-κB axis suppressed	2 mg per mouse	N1	[39]
Oleandrin	mice/in vivo	Bmal1iKO, Bmal1fl/fl, and WT C57BL/6 mice were housed under a 12L:12D cycle (lights off at 7 PM)	↓ mdr1a mRNA and P-gp abrogated	4 mg/Kg	N1	[71]
Nerigoside	HT29 cell lines and SW620 cell lines /in vitro	Nerigoside treated HT29 cell lines and SW620 cell lines	NG suppresses CRC growth via ERK/GSK3β/β-catenin axis	0,100,200, and400 nM	N1	[43]
PBI-05204	Panc-1 and Capan-II cells/in vitro	PBI-05204 treatment on Panc - 1/Capan - II cells	Down-regulatingPI3K/Akt/mTOR exerts anti-tumor activity	10 and 20 mg/Kg	N1	[72]
hydroalcoholic extract from the leaves of *Nerium oleander*	A549 cell line, HT29 cell line/in vitro	*Nerium oleander* hydroalcoholic extract (NOE) treated A549 and HT29 cells	Induction of anticancer effects in lung cancer patients	320μg/mL or 4h and 24h	N1	[73]

	Extract of the pink flowers of *Nerium oleander*	Caco-2 and HT29 cell lines/in vitro	Extract of the pink flowers of *Nerium oleander* treated Caco-2 and HT29 cell lines	Inhibition of proliferation of colorectal cancer cell lines	1.953-125µg/mL	N1	[46]
	N. oleander methanolic extract	HT-144, MCF-7, NCI-H460 and SF-268 cell lines /in vitro	*N. oleander* methanolic extract treated HT-144, MCF-7, NCI-H460 and SF-268 cell lines	significant antiproliferative effects against the aforementioned cell lines	50µM	N1	[74]
Anti-diabetic activity	distillated *Nerium oleander*	Rats/in vivo	Type 2 diabetes model with streptozotocin and high-fat diet	Prevention of potential action prolongation caused by type 2 diabetes	375 µg/0.5 mL of distilled water	N1	[50]
	distillated *Nerium oleander*	Rats/in vivo	Type 2 diabetes model with streptozotocin and high-fat diet	↓ FBG, HbA1c, IR, TC, LDL, AI, TG/HDL ratio, insulin & leptin	3.75, 37.5, and 375 µg/0.5mL of distilled water	N1	[51]
	Nerium oleander Stem and root extracts	mice/in vivo	Tetracycline-induced diabetes mellitus in mice	↓ HbA1c, liver glycogen, lipids and organ injury markers	200 mg/BW	N1	[48]

	ethanolic Nerium flower extract	rats /in vivo	Streptozotocin STZ induced diabetic rats	↓ HbA1c and ↑ SLC2A2	25,75,225 mg/kg/day	N1	[49]
cardiotonic activity	Hydroethanolic Extract of *Nerium Oleander* flower	Rat/in vivo	Rat model of isoprenaline-induced cardiotoxicity	improve the antioxidant defense system	10,30,100 mg/kg	N1	[54]
Hepatoprotective activity	70% hydroethanolic extract of the dried leaves (NO)	HepG 2 cells /in vitro	lipopolysaccharide (LPS)-treated HepG2 cells	reduced systemic inflammation, serum lipid peroxidation byproducts, and glucose	25μg/mL	N1	[56]
	Hydro-methanolic extracts of oleander stem and root	mice/in vivo	CCL_4 induced toxicity mice	↑ Hepatic CAT and POD activity, ↓ TNF-α	250,500,1000,2000 mg/kg	N1	[57]
	Nerium indicum leaf extract	mice/in vivo	CCL_4 induced mice liver injury	The intracellular biochemical indicators have significantly returned to normal.	250,500,1000,2000 mg/kg	N1	[47]

Anti-inflammatory activity	70% hydro-methanolic extract of *Nerium indicum* leaves	mice/in vivo	Treatment of inflammatory diseases	↑ IL-2, IFN-γ, IL-10, ↓ IL-4, TNF-α	50,100 mg/kg	N1	[58]
	Nerium oleander ethanolic flower extract	rats/in vivo	Cotton ball-induced granuloma, carrageenan gum-induced foot edema in rats	↓NO, PGE_2, TNF-α, IL-1β; ↓iNOS, TNF-α, IL-1β, Cox-2	20,30 mg/mL	N1	[59]
	Oleandrin	HeLa (human epithelial cells) /in vitro	Oleandrin treated human epithelial cells	Oleandrin blocked ceramide-induced NF-kB activation and potentiation of apoptosis.	0.2 mg/mL	N1	[60]
	odoroside A	Human lung carcinoma A549 cells /in vitro	odoroside A treated human lung carcinoma A549 cells	Prevent NF-kB-inducible protein expression by blocking the Na^+-dependent amino acid transport.	/	N1	[61]
	Nerium Oleander leafextract	rats/in vivo	burn alone rats	↓ MDA, ↑ GSH, ↓ MPO, ↓ TNF-α, ↓ IL-1β	/	N1	[75]

Anti-viral activity	oleandrin or *Nerium oleander* extract	SLB1 lymphoma T-cell-line /in vitro	oleandrin or *Nerium oleander* extract treated SLB1 lymphoma T-cell-line	Inhibition of virological synapse formation and HTLV-1 transmission in vitro.	10,50,100 μg/mL	N1	[63]
	hot extract and cold extract (breastin) of *Nerium oleander*	Poliovirus type 1 (PV1) /in vitro	hot extract and cold extract (breastin) of *Nerium oleander* treated (PV1)	Inhibit PV1 virus infection	/	N1	[65]
	Aqueous extract of *Nerium oleander* （Anvirzel™）	The human cell line HeLa CD4-LTR/β-gal /in vitro	Aqueous extract of *Nerium oleander*（Anvirzel™） treated the human cell line HeLa CD4-LTR/β-gal	Reduce expression of the envelope protein gp120.	0.1 – 10 μg/mL	N1	[63]
Anti-oxidant activity	Extract of the pink flowers of *Nerium oleander*	HT29 cells and Caco-2 cells /in vitro	Extract of the pink flowers of *Nerium oleander* treated HT29 cells and Caco-2 cells	Ability to reduce peroxyl radicals and inhibit the proliferation of colorectal cancer cell lines	1.953-125 μg/mL	N1	[46]
Hypolipidemic activity	ethanolic extract of flowers of *Nerium oleander*	Rats /in vivo	High-fat diet (HFD)-induced rats	↓ Weight gain, lipids; ↑ HDL (plasma/heart)	/	N1	[76]

Neuroprotective activity	Polysaccharides isolated from *Nerium indicum*	Beta amyloid induced neuronal cells /in vitro	*Nerium indicum* polysaccharides in Aβ-treated neuronal cells	Nerium Indicum targets JNK to rescue Alzheimer's neurons	20,40,100,250, 500 μg/mL	N1	[69]
Skeletal muscle diastolic activity	Aqueous extract of *Nerium oleander* flowers (AENOF)	Swiss albino rats/in vivo	Induction of muscle relaxation in rats by rotating rod and Actophotometer	Reduced the motor coordination of the tested animals.	0.5,1.0,2.0 g/kg	N1	[77]

N1: *Nerium oleander* L.(Nerium indicum); N2: *Nerium indicum mill.cv* Paihua

6. Constitutive Relationship of Antitumor Effects of Chemical Constituents in *N. oleander*

6.1 Constitutive Relationship of Antitumor Effects of Cardiac Glycosides

6.1.1 Type of Linked Glycoside at C_3-Position

Yuan-Lin Cao et al. isolated cardiac glycosides from *N. oleander*, among which oleandrigenin-3-*O*-*β*-*D*-diginopyranoside (**24**) and 3*β*-*O*-(*β*-*D*-sarmentosyl)-16*β*-acetoxy-14-hydroxy-5*β*,14*β*-card-20(22)-enolide (**34**) exhibited inhibitory effects on GT cells with IC_{50} values of 0.29 and 0.03 μM, respectively. It was found that compound **34** demonstrated a potent inhibitory effect, suggesting that the linkage of a β-D-sarmentosyl glycoside at the C_3-position significantly enhances the inhibitory activity against cancer cells [6].

6.1.2 The Relative Configuration of The Hydrogen Bond at the C_5-Position

Yuan-Lin Cao et al. isolated odoroside A (**2**) with a β-H at the C_5-position and odoroside B (**3**) with an α-H at the C_5-position from *N. oleander*. They investigated the cytotoxic effects of these compounds on various cancer cell lines, including HCT116, HT29, SW620, RKO, GT, and HELA. The IC_{50} values are presented in Table S4. The results showed that odoroside A exhibited stronger activity, indicating that cardiac glycosides with a β-H at the C_5-position had more pronounced inhibitory effects on cancer cells than those with an α-H [6].

6.1.3. The Carboxyl Group Linked at C_{17}-Position of Triterpenoids

It has been found that the presence of a carboxyl group in triterpenoids also affects the anti-tumor activity of *N. oleander*. Ursane-type triterpenoids, including ursolic acid (**102**) and urs-12-ene-3,28-diol (**107**), along with lupane - type triterpenoids, such as betulinic acid (**96**) and betulin (**97**), were isolated from *N. oleander*. They investigated the induction of ICAM-1 and the inhibitory effects on human lung cancer A549 cells. The IC_{50} values were 21.6 μM, >316 μM, 72.8 μM, and >316 μM, respectively. The results showed that ursolic acid and betulinic acid exhibited a certain degree of inhibitory activity, while urs-12-ene-3,28-diol and betulin did not show significant inhibitory effects on the induction of ICAM-1 or the proliferation of A549 cells. Based on structural analysis, the inhibitory activity may be related to the presence of a carboxyl group, rather than the structural type of the triterpenoid [20].

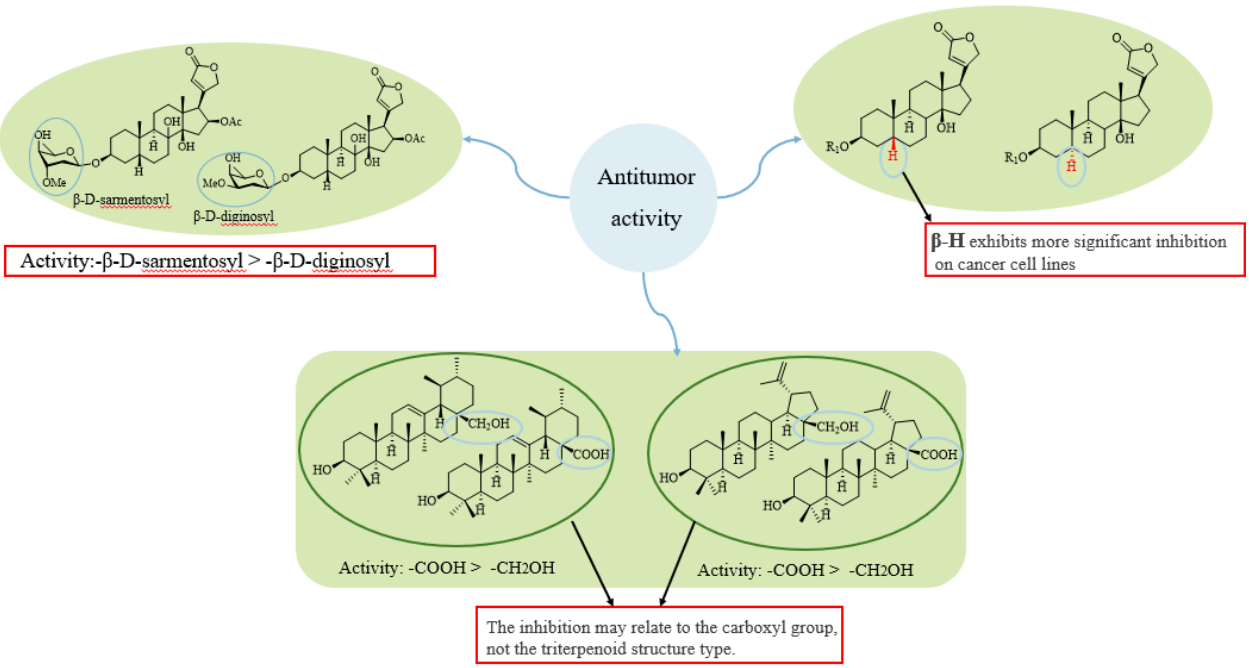


Figure 9. Relationship between chemical constituents and antitumor activity in *Nerium oleander* L.

7. Pharmacokinetics

The pharmacokinetics of oleandrin was investigated in mice via oral and intravenous administration. After oral dosing, oleandrin was swiftly taken up, reaching the maximum plasma concentration (C_{max}) within 20 minutes. The oral bioavailability of the substance was around 30%. Moreover, when compared with the situation after intravenous administration, its elimination half-life was longer. Following intravenous injection, oleandrin was detected in the liver, heart, and kidneys, with a notably higher concentration in the liver. Most of the administered oleandrin was excreted in the feces. Moreover, subsequent detection following the intraperitoneal injection of N. oleander extract or oleandrin indicated that specific components within the N. oleander extract could potentially facilitate the transportation of oleandrin across the blood-brain barrier [86]. Due to cows accidentally ingesting feed containing oleander, Ceci et al. conducted detections using ultra - high performance liquid chromatography - tandem mass spectrometry (UHPLC - MS/MS). They found that oleandrin was present in samples of serum, liver, heart, milk, and cheese. The results indicated that after entering the cows' bodies, oleandrin was distributed to multiple tissues and organs [87]. The pharmacokinetics of periplocin following oral administration in mice were investigated at two distinct circadian time points, ZT 2 and ZT 10. UPLC-MS/MS analysis revealed a significant influence of dosing time on pharmacokinetic behavior, with higher drug exposure (AUC) observed after ZT 2 administration compared to ZT 10 [88].

8. Quality Control Studies

Quality control of traditional Chinese medicine (TCM) was a crucial step in ensuring its safety, efficacy, stability, and controllability. Xie Yang jiao and colleagues conducted studies on the morphological, thin-layer chromatographic, and microscopic identifications of oleander. They also measured the moisture content, total ash, acid - insoluble ash, and extractives of *N. oleander*

[89]. Furthermore, advanced analytical techniques such as chromatography, mass spectrometry, and UPLC-MS/MS can be employed for the quantitative analysis of bioactive compounds in *N. oleander*. Liu Xu established HPLC-UV and HPLC-MS/MS methods to develop chromatographic fingerprint profiles of *N. oleander* samples from different geographical origins and preliminarily identified their active constituents. Singh et al. employed ultra – high performance liquid chromatography - electrospray ionization - mass spectrometry/mass spectrometry (UHPLC - ESI - MS/MS) to quantitatively determine three chemical markers in *N. oleander*, namely odoroside H (244.8 μg/g), odoroside A (231.4 μg/g), and oleandrin (703.9 μg/g). And it was found that there was a seasonal variation in its cumulative content, in which odoroside A (summer, stems) > odoroside H (winter, stems) > oleandrin (rainy, leaves), which provided a reference for the selection of harvesting season [90].

9. Application

Heart failure results from the impairment of the heart's pumping function, causing the heart to fail to satisfy the body's fundamental metabolic requirements. A study found that after 83 heart - failure patients took *N. oleander* leaf capsules prepared by different methods, the effective rate reached 75% [91]. Li Xing yu conducted a study on using *N. oleander* leaves to treat 20 patients with heart failure. Among them, 19 patients were effectively treated [92]. The main adverse reactions included nausea, vomiting, dizziness, and cardiac adverse events. These adverse reactions could be controlled by discontinuing the medication or taking oral potassium chloride. In addition, low- dose oleander can be used to treat diabetes and hypertension [93]. It is also effective in treating traumas such as burns and cuts [94]. When using oleander for treatment, it's crucial to be aware of its contraindications. The primary bioactive constituents of *N. oleander* are cardiac glycosides, with digitoxin being the primary type. It is not advisable to use it in combination with other cardiac glycoside - based drugs such as digoxin. Concurrent use will lead to a potent cardiotonic effect and toxic reactions [95]. Moreover, *N. oleander* is prohibited from being combined with excitable myocardial β such as ephedrine, calcium ions and other drugs. Simultaneous use will lead to increased toxicity, arrhythmia and heart failure [96].

In addition to its application in the field of medicine, *N. oleander* can be used as an insecticide. El-Akhal et al. have studied that the ethanol extract of *N. oleander* can kill the larvae of Culex pipiens. The concentrations corresponding to LC50 and LC90 are 57.57 mg/mL and 166.35 mg/mL, respectively. The results show that the extract of *N. oleander* can be used as an effective natural insecticide for potential mosquito larvae [97]. Researchers found that *N. oleander* leaf extracts could be effectively employed to synthesize silica nanoparticles (SiO_2 NPs) for antibiotic wastewater treatment, significantly enhancing tetracycline (TC) adsorption efficiency on the nanoparticle surfaces [98]. Furthermore, *N. oleander* is widely cultivated as an urban landscaping plant due to its vibrant blooms, extended flowering period, and smoke/dust-resistant foliage [99][100]. Beyond ornamental use, its seeds serve as a source of lubricating oil, while the bark fibers possess sufficient tensile strength for textile blending applications [2].

10. Conclusion

In terms of botany, phytochemistry, pharmacological effects, toxicity, and the structure-activity link between its chemical ingredients and anti-tumor activity, this report

provides a systematic summary of the advancements in *N. oleander* research. So far, 146 compounds have been separated and identified from *N. oleander*, chiefly incorporating cardiac glycosides, triterpenoids, and phytosterols. Modern pharmacological research indicates that *N. oleander* has pharmacological effects such as anti-tumor, anti-diabetic, cardiotonic, hepatoprotective, anti-inflammatory, anti-viral.

Cardiac glycosides are the most important active constituents in *N. oleander*, characterized by an unsaturated lactone ring connected at the C_{17}-position, which is directly related to the anti-tumor activity of *N. oleander*. For example, oleandrin (**1**) has shown significant anti-tumor effects. However, most current research is limited to cell activity screening and in vivo and in vitro experiments in mice. Therefore, in the future, research efforts should be centered on clinical trials and a more in-depth exploration of the cardiac glycosides in *N. oleander*. According to structure-activity relationships, the types of connected to the glycosides and the orientation of hydrogen bonds are related to their pharmacological activities. Thus, structural modification of less active compounds is necessary.

In clinical applications, *N. oleander* is employed in the management of heart failure, diabetes, hypertension, and trauma. Therefore, when using oleander in clinical practice, it is essential to strictly control the dosage, pay attention to its contraindications, and avoid patients developing arrhythmia or even death. Further studies should be able to focus on strategies such as structural modification, co-administration, and the development of new formulation dosage forms such as nanotechnology, so that it can maintain its efficacy while reducing its toxic effects. And it can focus on the use of analytical techniques such as chromatography and mass spectrometry for the determination of the content of the active constituents of *N. oleander*, in-depth exploration of its extraction process, and enhancement of its quality control.

Author contributions

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

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Competing Interests

The authors declare that there is no conflict of interest.

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