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Review

Daphnane-type diterpenes from genus *Daphne* and their anti-tumor activity

Zi-lin Hou, Guo-dong Yao *, Shao-jiang Song

Liaoning Key Laboratory of Computational Chemistry-Based Natural Antitumor Drug Research & Development, School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, Shenyang 110016, China

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ABSTRACT

Daphnane-type diterpenenoids are the major biologically active constituents in the genus *Daphne*. We find that there are about 101 Daphnane-type diterpenes in this genus, most of those compounds show different degrees of inhibitory effect on various cancer cell. Some of them have been studied in depth and the potent molecular mechanisms might be associated with modulation of different cell-signaling pathways. In addition, some compounds of this type also can inhibit the synthesis of protein and DNA. Absolutely, the anti-tumor activity of Daphnane-type diterpenes is worthy of attention. Unfortunately, most of the current research on the activity of these compounds is focused on simple drug efficacy, and its in-depth mechanism research is far from enough. On the other point of view, there still exists wide growing space on the depth of these compounds.

Contents

* Corresponding author.
E-mail address: guodong_yao@126.com (G.-d. Yao).

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1. Introduction

The genus *Daphne* includes about 95 species found mainly in Asia and Europe. It is well known for its Greek mythology and the medicinal usage in different ethnic cultures over the world (Zhan et al., 2005). The genus plays an important role in the medicine development from ancient to modern time. For example, *Daphne genkwa* Sieb. et Zucc. is a toxic shrub widespread in China and Korea. As a folk medicine, its flower buds are used as for purge water and expel phlegm to relieve cough, kill insects and cure sores. Records from the *Compendium of Materia Medica* and *Drug Properties in Verse* showed that *D. genkwa* had the effect of detoxication. In the Chinese Pharmacopoeia, the medical parts originate from the leaves, flowers or roots of *Daphne odora* Thunb. It was used as a traditional medicine for wind-damp-dispelling, promoting blood circulation and relieving pain. Obviously, these drugs mainly achieve the purpose of treating diseases via dispelling toxins and stimulating the blood vessels, and this just coincides with the view of traditional Chinese medicine treatment of tumor.

Several scholars have concentrated on the chemical composition and bioactivities of genus *Daphne*. Previous phytochemical studies of this genus have shown the presence of flavonoids (Du et al., 2016), lignans (Zhang et al., 2018) and diterpenenoids (Zhan et al., 2005). All of these, Daphnane-type diterpenenoids are the major biologically active constituents (Zhan et al., 2005). Previous pharmacological researches demonstrated that the type of these compounds bear a wide range of biological activities including anti-tumor, anti-inflammatory, neurotrophic and anti-HIV activities (Han et al., 2016; Yin et al., 2018; Zhang et al., 2018).

Several reviews are available but none of them covers the development of the last decades (Liao et al., 2009; He et al., 2002), which have witnessed enormous progress in the discovery of structural types, as well as the knowledge of the molecular basis underlying the biological activity of these compounds. This review aims at filling this gap, providing a detailed list of the compounds isolated so far and a systematic summary uncovered the anti-tumor activity and related molecular mechanism, in order to find a suitable breakthrough for further development and utilization of this type of compound.

2. Compound structures

Daphnane-type diterpenoids usually embrace a 5/6/7-tricyclic ring system with poly-hydroxyl group and most of them have a characteristic orthoester function located at ring C. According to the oxygen containing functions at ring B and ring C, and the substitution pattern of the ring A compounds of this structural, Daphnane-type diterpenoids that come from this genus can be categorized into daphnetoxins, 12-hydroxydaphnetoxins, 1-alkydaphnanes, genkwanines and resiniferonoids. Additionally, some Daphnane-type diterpenoids have no typical structural features and do not belong to above groups, which are categorized as an independent class (Liao, Chen et al., 2009) (Figs. 1 and 2, Fig. S1, Table 1).

3. Cytotoxicity

Previous pharmacological studies showed that Daphnane-type diterpenes exhibit inhibitory effects on lung cancer, liver cancer, breast cancer, colon cancer and leukemia cells, and some of them have been tested for their activities in A549, HepG2, SMMC-7721, MCF-7, SK-BR-3, HCT116, SW480, HL-60 cells (Table S1) (Li et al., 2013). To make the results more intuitive, we use a heat map to describe this trend (Fig. 3).

4. Structure-activity relationship

Daphnane-type diterpenes have complex structures and rich functional groups, which can exert an influence on their biological activity. This paper roughly analyzed and summarized the relationship between the structure and activity of these compounds (Liao, et al. 2009). According to the difference of rings A, B, C and the location of substituents, combined with literature reports we described the structure–activity relationship as follows (Fig. 4).

5. Molecular mechanism

Regarding the high biological activity of some Daphnane-type diterpenes and as part of our screening program to evaluate the potential chemotherapeutic effects of natural compounds, we have mapped their pharmacological mechanisms of action. The methods adopted by different researchers in the study of the activity of these compounds are not completely consistent. In order to make it clear and preciseness we describe these on the supporting information (Figs. S2–S5).

5.1. Lung cancer

5.1.1. Yuanhuadine inhibits Akt/mTOR pathways

When treated with Yuanhuadine, the activation of ERK1/2 and Akt was suppressed. Furthermore, the phosphorylation of Akt

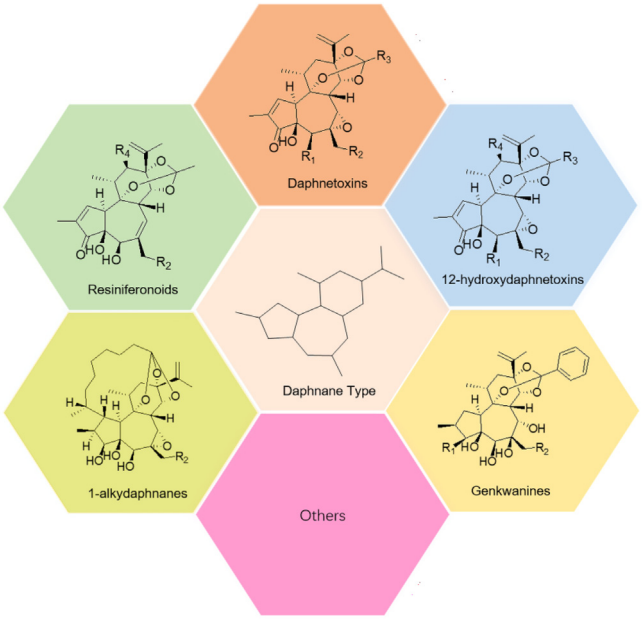


Fig. 1. Classes of Daphnane-type diterpenoids from genus *Daphne*.

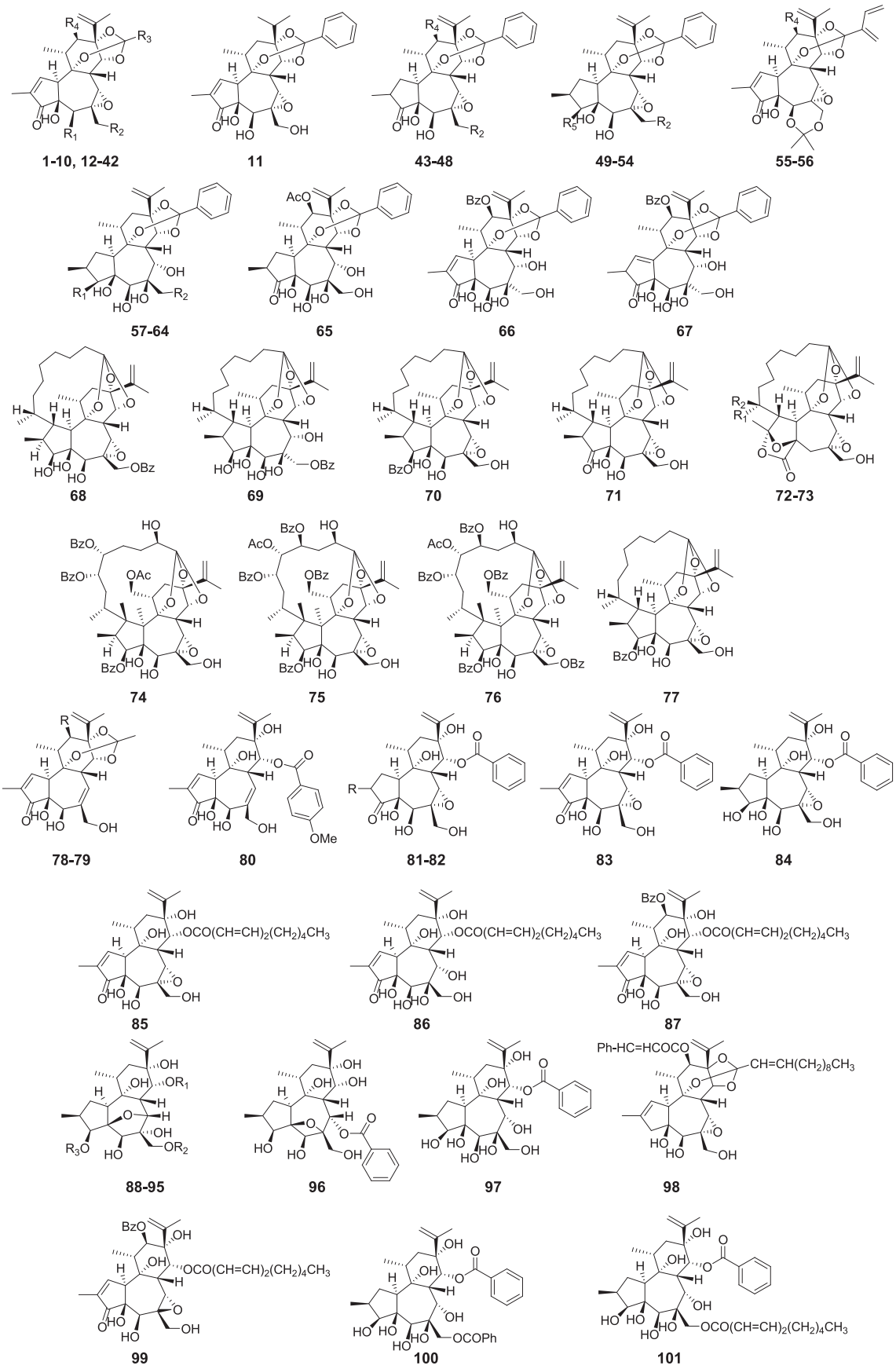
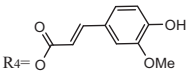
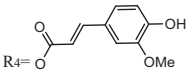
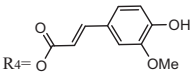
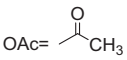


Fig. 2. Chemical structures of daphnetoxins (**1**–**11**), 12-hydroxydaphnetoxins (**12**–**56**), genkwanines (**57**–**67**), 1-alkyldaphnanes (**68**–**77**), resiniferonoids (**78**–**80**) and others (**81**–**101**).

Table 1
Chemical structures and sources of Daphnane-type diterpenoids (**1**–**101**).

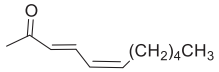
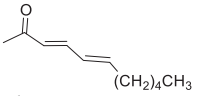
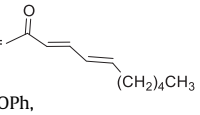
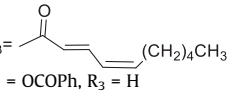
No.	Compounds	Chemical structures	Original plants
1	Daphnetoxin	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = H	D. *mezereum* (Ronlán & Wickberg, 1970)
2	Daphnegiraldifin	R_1 = OH, R_2 = $OCO(CH_2)_{14}CH_3$, R_3 = Ph, R_4 = H	*D. giraldii* (Liao et al., 2009)
3	Daphne factor F1	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH_2)_8CH_3$, R_4 = H	*D. papyrecea* (Wu et al., 1994, 1993)
4	Excoecaria factor O1	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_3(CH_2)_2CH_3$, R_4 = H	*D. autiloba* (Adolf et al., 1985)
5	Excoecariatoxin	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH_2)_4CH_3$, R_4 = H	*D. autiloba* (Wang et al., 1981; Powell et al., 1985; Bala et al., 1999)
6	Tanguticamin	R_1 = OH, R_2 = OCOCH = $CH(CH_2)_{14}CH_3$, R_3 = Ph,R_4 = H	*D. tangutica* (Liao, Chen & Yue, 2009)
7	Tanguticalin	R_1 = OH, R_2 = $OCO(CH_2)_{16}CH_3$, R_3 = Ph, R_4 = H	*D. tangutica* (Liao, Chen & Yue, 2009)
8	14′-Ethyltetrahydrohuratoxin	R_1 = OH, R_2 = OH, R_3=$(CH_2)_{14}CH_3$, R_4 = H	*D. autiloba* (Adolf et al., 1988)
9	Simplexin	R_1 = OH, R_2 = OH, R_3=$(CH_2)_8CH_3$, R_4 = H	*D. tangutica* (Powell et al., 1985)
10	Invesiculosin	R_1 = OH, R_2 = OAc, R_3 = Ph, R_4 = H	*D. tangutica* (Liao, Chen & Yue, 2009)
11	Tangutcahin		*D. tangutica* (Liao, Chen & Yue, 2009)
12	12-Hydroxydaphnetoxin	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = OH	*D. mezereum* (Ronlán & Wickberg, 1970)
13	Gniditrin	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = $OCO(CH = CH)_3(CH_2)CH_3$	*D. giraldii* (Kupchan et al., 1975)
14	Gnidicin	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = OCOCH-Ph	*D. giraldii* (Kupchan et al., 1975)
15	Gnididin	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = $OOC(CH = CH)_2(CH_2)_4CH_3$	*D. giraldii* (Kupchan et al., 1975)
16	Daphnegiraldidin	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = $OCO(CH_2)_{10}CH_3$	*D. giraldii* (Liao, Chen & Yue, 2009)
17	Acutilobin A	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = $OCO(CH = CH)_2COC(CH_2)_2CH_3$	*D. autiloba* (Huang et al., 2012)
18	Acutilobin B	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = $OCO(CH = CH)_3C(OH)CH_2CH_3$	*D. autiloba* (Huang et al., 2012)
19	Genkwadaphnine	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = OCOPh	*D. genkwa* (Kasal, Lee & Huang, 1981)
20	Yuanhuajine	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_3(CH_2)_2CH_3$, R_4 = OCOPh	*D. genkwa* (Zhang et al., 2006)
21	Kirkinine	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_3(CH_2)_2CH_3$, R_4 = OAc	*D. autiloba* (He et al., 2000)
22	Gnidilatin	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH_2)_4CH_3$, R_4 = OCO-Ph	*D. oleoide* (Ullah et al., 2001)
23	Mezerein	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = $OCO(CH = CH)_2Ph$	*D. mezereum* (Ronlán & Wickberg, 1970)
24	Yuanhuaoate A	R_1 = OH, R_2 = OH, R_3 = Ph, R_4 = OAc	*D. genkwa* (Zeng et al., 2009)
25	Yuanhuahine	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH_2)_4CH_3$, R_4 = $OCOCH_2CH_3$	*D. genkwa* (Hong, Nam, Seo & Lee, 2010)
26	Yuanhualine	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH_2)_4CH_3$, R_4 = $OCO(CH_2)_2CH_3$	*D. genkwa* (Hong, Nam, Seo & Lee, 2010)
27		R_1 = OH, R2 = OH, R_3=(CH = CH)3(CH2)2CH3, R_4 = OCOCH = CHPh	*D. odora* (Hajime, Mitsuru et al., 1982)
28		R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH2)_4CH_3$, R_4 = OCOCH = CHPh	*D. odora* (Hajime et al., 1982)
29	Yuanhuacine	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH_2)_4CH_3$, R_4 = OCO-Ph	*D. genkwa* (Wang et al., 1981)
30	Isoyuanhuacine	R_1 = OH, R_2 = OH, R_3=$(CH = CH)(CH = CH)(CH_2)_4CH_3$, R_4 = OCO-Ph	*D. genkwa* (Wang et al., 2018)
31	Yuanhuadine	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH_2)_4CH_3$, R_4 = $OCOCH_3$	*D. genkwa* (Liao, Chen & Yue, 2009)
32	Yuanhuagine	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_3(CH_2)_2CH_3$, R_4 = $OCOCH_3$	*D. genkwa* (Zhang et al., 2006)
33	Genkwadane D	R_1 = OH, R_2 = OH, R_3=$(CH = CH)_2(CH_2)_4CH_3$, R_4 = $OCOCH(CH_3)_2$	*D. genkwa* (Li et al., 2013)
34	5-Hydroxyresiniferonol-6R,7Repoxy-12-acetoxy-9,13,14ortho-2E-decenoate	R_1 = OH, R2 = OH, R_3 = CH = CH(CH2)6CH3, R_4 = OCOCH3	*D. genkwa* (Akhtar, Khan & Ali, 2006)
35	Tanguticacin	R_1 = OH, R_2 = $OOC(CH_2)_{14}CH_3$, R_3 = Ph, R_4 = $OOC(CH = CH)_3(CH_2)_2CH_3$	*D. tangutica* (Liao, Chen & Yue, 2009)
36	Tanguticagin	R_1 = OH, R_2 = $OCO(CH_2)_{14}CH_3$, R_3 = Ph, R_4 = OCOCH = CH-Ph	*D. tangutica* (Akhtar, Khan & Ali, 2006)
37	Genkwadaphnin-20-palmitate	R_1 = OH, R_2 = OCO(CH2)14CH3, R_3 = Ph, R_4 = OCO-Ph	*D. oleoide*(Taninaka et al., 1999)
38	Gnidilatidin-20-palmitate	R_1 = OH, R_2 = $OCO(CH_2)_{14}CH_3$, R_3=	*D. oleoide*

Table 1 (*continued*)

No.	Compounds	Chemical structures	Original plants
		$(CH=CH)_2(CH_2)_4CH_3$, R_4 = OCO-Ph	(Yeşilada et al., 2001)
39	Gnidicin-20-palmitate	R_1 = OH, R_2 = $OCO(CH_2)_{14}CH_3$, R_3 = Ph, R_4 = OCOCH = CH-Ph	*D. oleoide* (Taninaka et al., 1999)
40	Acutilobin C	R_1 = OH, R_2 = OH, R_3=$(CH=CH)_3(CH_2)_2CH_3$, 	*D. autiloba* (Huang et al., 2012)
41	Acutilobin D	R_1 = OH, R2 = OH, R_3=$(CH=CH)_2(CH_2)_4CH_3$, 	*D. autiloba* (Huang et al., 2012)
42	Acutilobin E	R_1 = OH, R2 = OH, R_3 = Ph, 	*D. autiloba* (Huang et al., 2012)
43	Tanguticakin	R_2 = OH, R_4 = H	*D. tangutica* (Liao, Chen & Yue, 2009)
44	1,2α-Dihydrodaphnetoxin	R_2 = OH, R_4 = H	*D. genkwa* (Pan et al., 2010)
45	Daphne factor P2	R_2 = OH, R_4 = $OCO(CH=CH)_3(CH_2)_2CH_3$	*D. odora* (Tamura, 1979)
46	Yuanhuapine	R_2 = OH , R_4 = OAc 	*D. genkwa* (Hu et al., 1986)
47	Yuanhuatine	R_2 = OH, R_4 = OCOPh	*D. genkwa* (Zhan et al., 2005)
48	1,2α-Dihydro-20-palimoyldaphnetoxin	R_2 = $OOC(CH_2)_{14}CH_3$, R_4 = H	*D. tangutica* (Pan, Zhang & Ding, 2006)
49	Acutilobin F	R_5 = $OOC(CH=CH)_3(CH_2)_2CH_3$, R_2 = OH	*D. autiloba* (Huang et al., 2012)
50	Acutilobin G	R_5 = OOCCH = CH-Ph, R_2 = OH	*D. autiloba* (Huang et al., 2012)
51	Genkwanine M	R_5 = OH, R_2 = OBz 	*D. genkwa* (Li, Gao & Peng, 2010)
52	Genkwanine N	R_5 = OBz, R_2 = OH	*D. genkwa* (Li, Gao & Peng, 2010)
53	Genkwanine N-20-palmitate	R_5 = OCOPh, R_2 = $OCO(CH_2)_{14}CH_3$	*D. genkwa* (Jiang, Wang & Li, 2015)
54	Orthobenzoate 2	R_5 = OH, R_2 = OH	*D. genkwa* (Wu et al., 1994)
55	Tanguticadin	R_4 = $OCO(CH=CH)_3(CH_2)_2CH_3$	*D. tangutica* (Liao, Chen & Yue, 2009)
56	Tanguticafin	R_4 = OCOCH = CHPh	*D. tangutica* (Liao, Chen & Yue, 2009)
57	Genkwanine A	R_1 = OH, R_2 = OH	*D. genkwa* (Zhan et al., 2005)
58	Genkwanine B	R_1 = $OCO(CH=CH)_2(CH_2)_4CH_3$, R_2 = OH	*D. genkwa* (Zhan et al., 2005)
59	Genkwanine C	R_1 = $OCO(CH=CH)_3(CH_2)_2CH_3$, R_2 = OH	*D. genkwa* (Zhan et al., 2005)
60	Genkwanine D	R_1 = OCOPh, R_2 = OH	*D. genkwa* (Zhan et al., 2005)
61	Genkwanine E	R_1 = OH, R_2 = $OCO(CH=CH)_3(CH_2)_2CH_3$	*D. genkwa* (Zhan et al., 2005)
62	Genkwanine F	R_1 = OH, R_2 = $OCO(CH=CH)_2(CH_2)_4CH_3$	*D. genkwa* (Zhan et al., 2005)
63	Genkwanine G	R_1 = OH, R_2 = $OCO(CH=CH)(CH_2)_6CH_3$	*D. genkwa* (Zhan et al., 2005)
64	Genkwanine H	R_1 = OH, R_2 = OCOPh	*D. genkwa* (Zhan et al., 2005)
65	Genkwanine L		*D. genkwa* (Zhan et al., 2005)
66	Yuanhuaoate B		*D. genkwa* (Zeng et al., 2009)
67	Genkwadane A		*D. genkwa* (Li et al., 2013)
68	Genkwadane B		*D. genkwa* (Li et al., 2013)
69	Genkwadane C		*D. genkwa* (Li et al., 2013)
70	Gnidimacrin		*D. odora* (Otsuki et al., 2020)

(*continued on next page*)

Table 1 (*continued*)

No.	Compounds	Chemical structures	Original plants
71	Wikstroelide E		*D. genkwa* (Li et al., 2013)
72	Pimelotide A	$R_1 = CH_3$, $R_2 = H$	*D. genkwa* (Li et al., 2013)
73	Pimelotide C	$R_1 = H$, $R_2 = CH_3$	*D. genkwa* (Li et al., 2013)
74	Daphneodorin A		*D. odora* (Otsuki et al., 2020)
75	Daphneodorin B		*D. odora* (Otsuki et al., 2020)
76	Daphneodorin C		*D. odora* (Otsuki et al., 2020)
77	pimelea factor P2		*D. genkwa* (Li et al., 2013)
78	DaphneresiniferinA	R = $OCOCH_3$	*D. genkwa* (Bang et al., 2013)
79	DaphneresiniferinB	R = Ph	*D. genkwa* (Bang et al., 2013)
80	14-(P-methoxylphenol)-excoecainol		*D. autiloba* (Coetzer & Pieterse, 1972; (Huang et al., 1985)
81		R = $CH_3(\alpha)$	*D. tangutica* (Pan et al., 2010)
82		R = $CH_3(\beta)$	*D. tangutica* (Pan et al., 2010)
83	Daphnegiraldigin		*D. giraldii* (Su & Wu, 2014)
84	Genkwanine O		*D. genkwa* (Zhan et al., 2005)
85	Wikstroelide M		*D. acutiloba* (Zhang et al., 2014)
86	Daphne factor F3		*D. genkwa* (Wu et al., 1994, 1993)
87	Yuanhuaoate E		*D. genkwa* (Zhan et al., 2005)
88	Neogenkwanine A	R_1 = OCOPh, $R_2 = H$, $R_3 = H$	*D. genkwa* (Li et al., 2015)
89	Neogenkwanine B	$R_1 = H$, R_2 = OCOPh, $R_3 = H$	*D. genkwa* (Li et al., 2015)
90	Neogenkwanine C	R_1 = OCOPh, $R_2 = H$, $R_3 = GRP_3$ 	*D. genkwa* (Li et al., 2015)
91	Neogenkwanine D	R_1 = OCOPh, $R_2 = H$, $R_3 = GRP_2$ 	*D. genkwa* (Li et al., 2015)
92	Neogenkwanine E	$R_1 = H$, R_2 = OCOPh, $R_3 = GRP_2$ 	*D. genkwa* (Li et al., 2015)
93	Neogenkwanine F	$R_1 = H$, R_2 = OCOPh, $R_3 = GRP_3$ 	*D. genkwa* (Li et al., 2015)
94	Neogenkwanine G	R_1 = OCOPh, R_2 = OCOPh, $R_3 = H$	*D. genkwa* (Li et al., 2015)
95	Neogenkwanine I	$R_1 = H$, $R_2 = H$, $R_3 = H$	*D. genkwa* (Li et al., 2015)
96	Neogenkwanine H		*D. genkwa* (Li et al., 2015)
97	Genkwanine I		*D. genkwa* (Zhan et al., 2005)
98	Gnidilatimonoein		*D. mucronata* (Mianabadi & Yazdanparast, 2004)
99	Yuanhuaoate C		*D. genkwa* (Zeng et al., 2009)
100	Genkwanine K		*D. genkwa* (Zhan et al., 2005)
101	Genkwanine J		*D. genkwa* (Zhan et al., 2005)

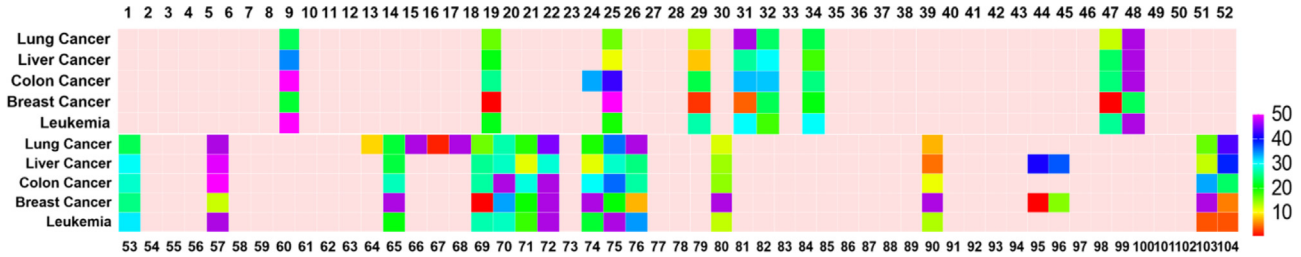


Fig. 3. Representation of activity trends in form of heatmap.

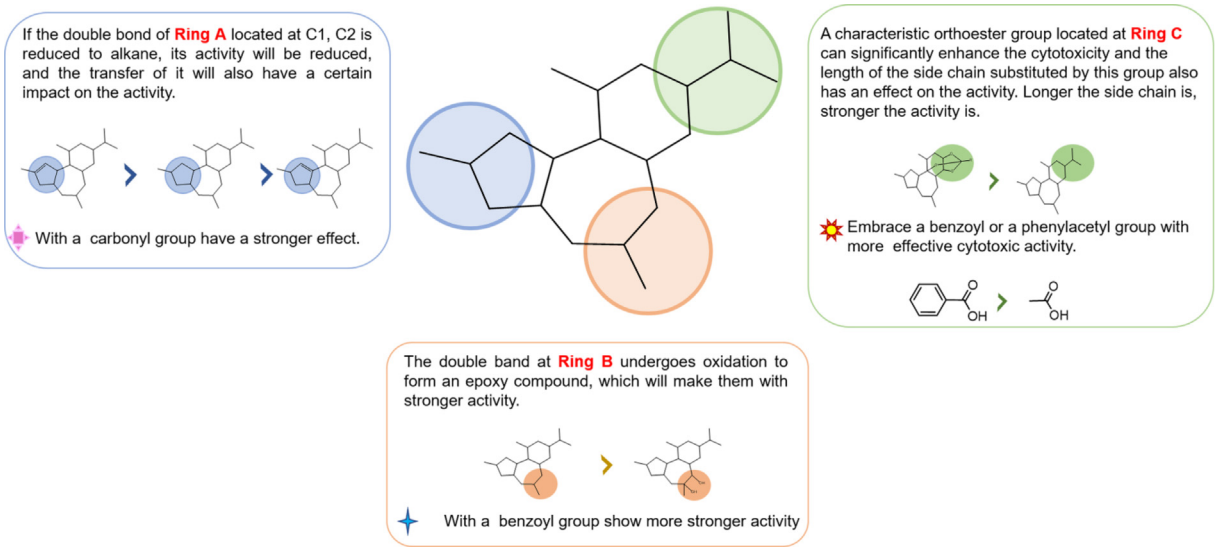


Fig. 4. Brief structure-activity relationships.

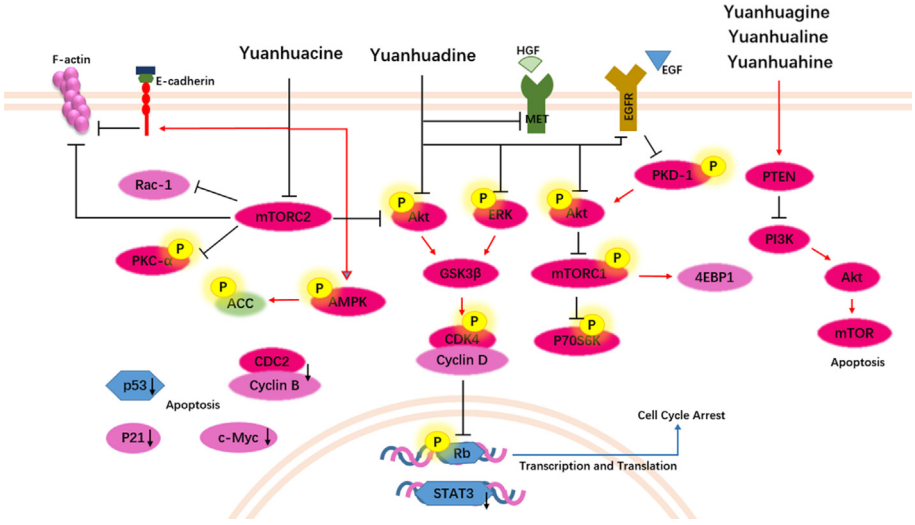


Fig. 5. Molecular mechanisms of Daphnane-type diterpenes on lung cancer.

upstream PDK-1 and its downstream effectors GSK3β and STAT3 were also inhibited. In addition, Yuanhuadine suppressed the phosphorylation of mTOR and its downstream effectors p70S6K and 4EBP1. Collectively, Yuanhuadine inhibits the antiproliferation of A549 cells by suppressing Akt/mTOR signaling pathways (Hong et al., 2011) (Fig. 5).

5.1.2. Yuanhuadine suppresses EGFR pathways

Research shows that the EGF-stimulated activation of EGFR was alleviated significantly when treated with Yuanhuadine in A549 cells (Hong et al., 2011). The activation of Akt and ERK1/2, downstream effectors of EGFR, was also inhibited by the compound. These results suggest that Yuanhuadine induce anti-proliferative

activity might be concomitant with the suppression of EGFR signaling pathways (Fig. 5).

5.1.3. Yuanhuadine prevents HGF/c-Met pathways

Research suggests that c-Met-dependent signaling in A549 cells is suppressed because Yuanhuadine can abrogate the HGF-induced auto-phosphorylation of c-Met (Hong et al., 2011). This may be a possible mechanism of action for the antiproliferative activity of Yuanhuadine (Fig. 5).

5.1.4. Effects of Yuanhuadine on checkpoint proteins

Yuanhuadine can arrest lung cancer A549 cells at the G0/G1 and G2/M phase, and these events were correlated with the expression of checkpoint proteins, such as CDK4, CDK2, cyclin E, cyclin A, c-Myc and so on (Hong et al., 2011). The event may be owing to the inhibition of Akt/GSK-3β or Akt/c-Myc signaling by Yuanhuadine. In addition, the down regulation of PDK-1 might enhance the negative regulation of the Akt signaling pathway by Yuanhuadine. The impact on G2/M phase cell-cycle arrest by Yuanhuadine was partially associated with the suppression of cyclin B1 and CDC2. (Fig. 5).

5.1.5. Yuanhuacine inhibits AMPK signaling pathway

After treatment with Yuanhuacine, the activation of mTORC2-associated downstream targets including Akt, protein kinase C alpha (PKC-α), ras-related C3 botulinum toxin substrate 1 (Rac1), and filamentous-actin (F-actin) was suppressed. Thus, Yuanhuacine could regulate AMPK/mTOR signaling pathway (Kang et al., 2015) (Fig. 5).

5.1.6. Yuanhuacine has an impact on actin cytoskeleton organization

Research has shown that Yuanhuacine effectively inhibit the invasion and migration of human non-small lung cancer H1993 cells, which can be ascribable to the actin cytoskeleton organization via downregulating F-actin and upregulating of E-cadherin (Kang et al., 2015) (Fig. 5).

5.1.7. Yuanhuadine could resistant gefitinib resistance

In H292-Gef cells, treatment with Yuanhuadine consequently resulted in SerpinB2 up-regulated and the lysosomal degradation of uPA then the proteolytic activity of MMP2 was inhibited. In addition, the expression of activated p38 and ERK (phosphorylated-p38 (p-p38) and p-ERK) was down-regulated in human non-small lung cancer cells treated with Yuanhuadine (Fig. 6).

Yuanhuadine through targeting the degradation of AXL receptor tyrosine kinase to overcome gefitinib resistance. Mechanistically, Yuanhuadine could induce the cleavage of AXL through the two sequential steps of presenilin-dependent regulated intramembrane proteolysis (RS-RIP), the ectodomain shedding and the intramembrane cleavage. Collectively, Yuanhuadine may accelerate the degradation of AXL, resulting in the reduction of full-length AXL expression and the half-life of AXL shorten (Bae et al. 2015) (Fig. 6).

5.2. Breast cancer

5.2.1. Yuanhuacine has an impact on apoptosis-regulated proteins

Bcl-2 family proteins act as vital regulators of apoptotic process (Czabotar et al., 2014). DNA usually degraded to fragments of low molecular weight when cells undergoing apoptosis, resulting a special DNA peak called Sub-G1. The celavege of caspase-3 and poly (ADP-ribose) polymerase (PARP) can also indicate that cells may undergone apoptosis. Yuanhuacine has been shown to induce apoptosis in breast cancer MCF-7 and myeloid leukemia HL-60 cells by modulating multiple signaling pathways (Li et al., 2013) (Fig. 7).

5.2.2. Yuanhuatine inhibits ERα pathway

There is no doubt, ERα is the most important disease target of breast cancer. Numerous cases have shown that Akt/mTOR and ERK/MEK signaling molecules are important downstream molecules of ERα (Saini et al., 2013; Zheng et al., 2015). As reports go, Yuanhuatine has an inhibitory effect on ERα and it down-stream signaling pathways (Zhang et al., 2019) (Fig. 7).

5.3. Colon cancer and bladder cancer

5.3.1. Yuanhuacine up-regulates expression of P21

According to the search, Yuanhuacine has an anti-tumor effect on bladder cancer T24T and colon cancer HCT116 cells, it could up-regulate p21 without an influence on p53, which was ascribable to that Yuanhuacine treatment could induce Sp1 protein, whereas it did not show an impact on p53 or STAT3 expression (Zhang et al., 2014). Yuanhuacine can activate p38 to stabilize Sp1 protein and, subsequently, leads to p21 transcription and protein expression. Collectively, Yuanhuacine induce inhibition of cell growth by up-regulating p21 protein expression in an p53-independent pathway (Figs. 8 and 9).

5.3.2. Genkwadaphnin blocks expression of PRDM1

Research shows that Genkwadaphnin could prominently induce the expression of the transcriptional repressor PRDM1 in human colon cancer SW620 cells (Kang et al., 2016). Furthermore, the con-

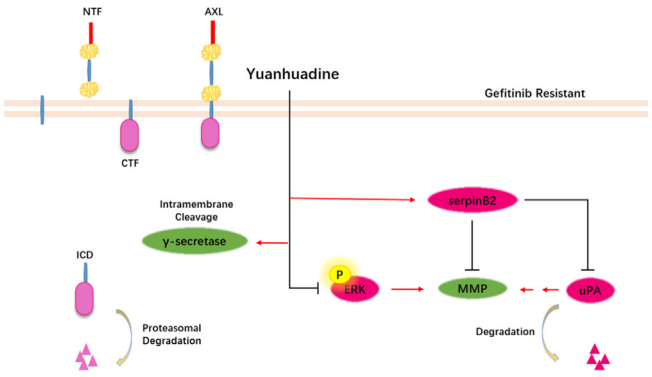


Fig. 6. Molecular mechanisms of Daphnane-type diterpenes on gefitinib-resistant cell.

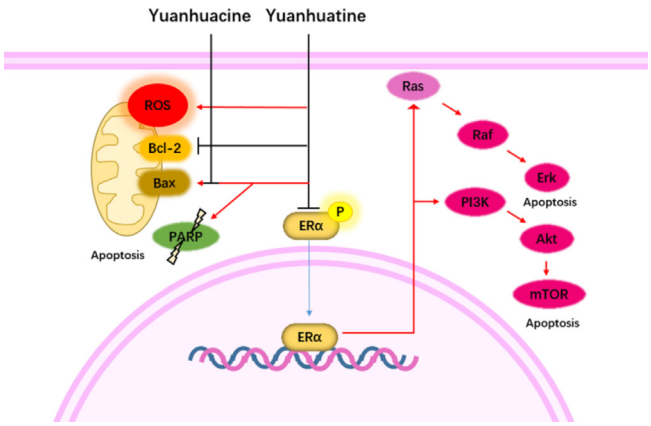


Fig. 7. Molecular mechanisms of Daphnane-type diterpenes on breast cancer.

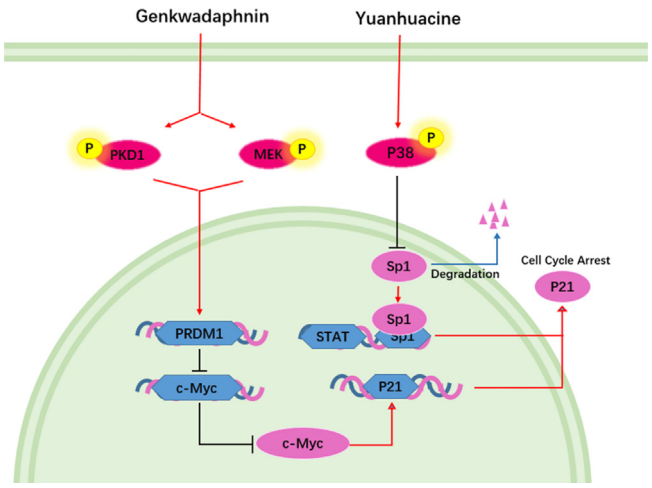


Fig. 8. Molecular mechanisms of Daphnane-type diterpenes on colon cancer.

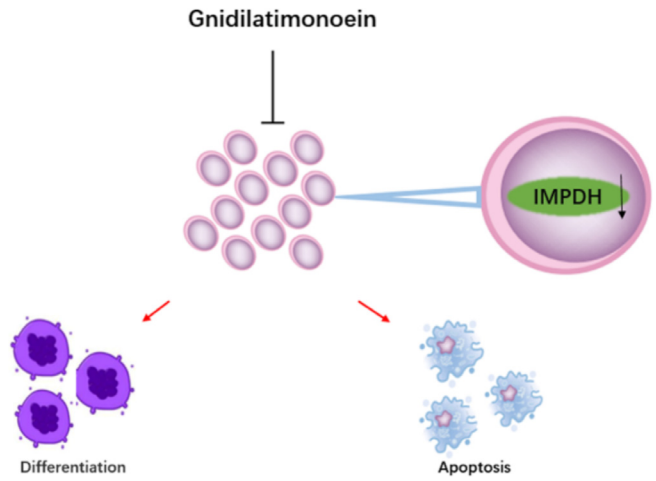


Fig. 10. Molecular mechanisms of Daphnane-type diterpenes on leukemia.

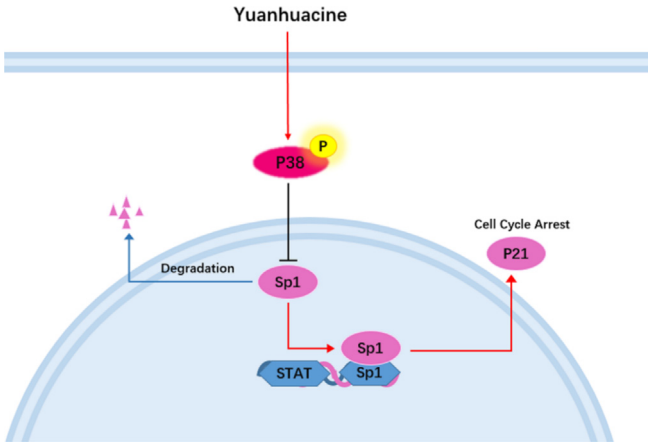


Fig. 9. Molecular mechanisms of Daphnane-type diterpenes on bladder cancer.

dition could enhancement via induce the phosphorylation of PKD1 and MEK, leading to the down-regulation of c-Myc and up-regulation of p21 subsequently. Thus, Genkwadaphnin has an anti-proliferative effect (Fig. 8).

5.4. Leukemia

5.4.1. Gnidilatimoein eliminates activity of IMPDH

As reports goes, Inosine monophosphate dehydrogenase (IMPDH) play a vital role in cell growth, differentiation, apoptosis and transformation (Cuny et al., 2017). Researches has clearly indicated that gnidilatimonoein, as a potent natural anti-proliferative and differentiation-inducing agent, exerts its delicate biological effects mainly through modulation of GTP pool size with the final subsequent effects on cellular DNA content (Nouri et al., 2011) (Fig. 10).

5.4.2. Yuanhuacine and Genkwadaphnin have influence on some biological macromolecules

According to the research, Yuanhuacine could inhibit the activity of DNA topoisomerase I and more important the effect is closely associated with the orthoester group. The reason is that the linkage area of DNA topo I has positive charge and the orthoester group happens to be an electron-donating group (Zhang et al., 2006). Other than this, protein synthesis is also inhibited after treatment with Yuanhuacine or Genkwadaphnin in P-388 cells (Zhang et al., 2006). They could block the elongation process and interference with the peptidyl transferase reaction. Mechanically, these compounds have a significantly inhibition on both the polyuridine-directed polyphenylalanine synthesis and the formation of the first peptide bond between puromycin and met-tRNA bound to the 80S initiation complex (Fig. 11).

5.5. Melanoma

Gnidilatidin can decrease expression of metastasis associated proteins. Researches show that gnidilatidin could decrease the expression of MMP9, MMP2 and CD44. Beyond that, Id2 (inhibitor of DNA binding 2) and Syt2 (synaptogaminlike 2) were also suppressed, which closely associated with tumor cell migration and invasion. In addition, Egr1 (early growth response 1), a cancer suppressor gene was up-regulated after treatment with gnidilation. Gnidilation inhibited the expression of MITF, and the expression of Mitf-regulated genes important for melanogenesis such as tyrosinase (Tyr), tyrosinase-related protein 1 (Trp 1), and dopachrome tautomerase (Dct), as well as the melanosome transport protein Rab27a were also decreased (Villareal et al., 2018) (Fig. 12).

In short, Daphnane-type diterpenes, come from *Daphne* L. (Thymelaeaceae), have prominent medicinal properties which can play an important effect on some relevant signaling pathways. To make it more intuitive, we describe it graphically (Fig. 13).

Other than this, Daphnane-type diterpenes also with mitochondrial toxicity (Diogo et al., 2009) (Fig. 14). Researches have shown that Daphnetoxin presented an effect on the function of mitochondrial including increased proton leak in the inner mitochondrial membrane, increased induction of the mitochondrial permeability transition pore, inhibition of ATP synthase and inhibition of the mitochondrial respiratory chain.

6. Conclusion and prospect

Natural products and their derivatives are primary sources of anticancer agents with novel mechanisms. Traditional medicine has been considered as the mainstay for the resource sourcing of natural products. Plants of genus *Daphne* are of great importance due to their outstanding therapeutic and medicinal usage in different ethnic cultures over the world. Daphnane-type diterpenenoids is the charactistic component of the genus. Our review shows that there are 101 Daphnane-type diterpenenoids in the genus, some of

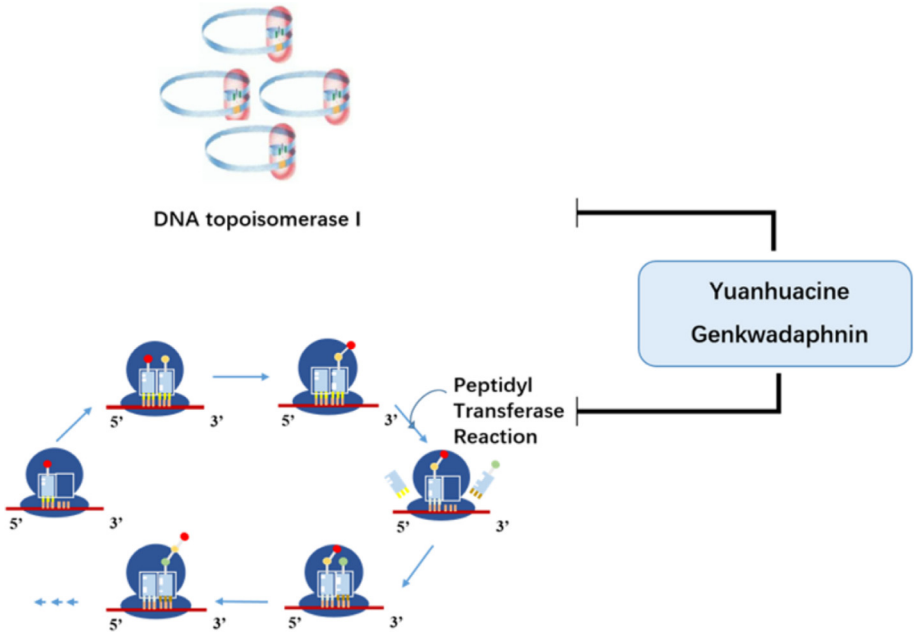


Fig. 11. Molecular mechanisms of Daphnane-type diterpenes on biological macromolecules.

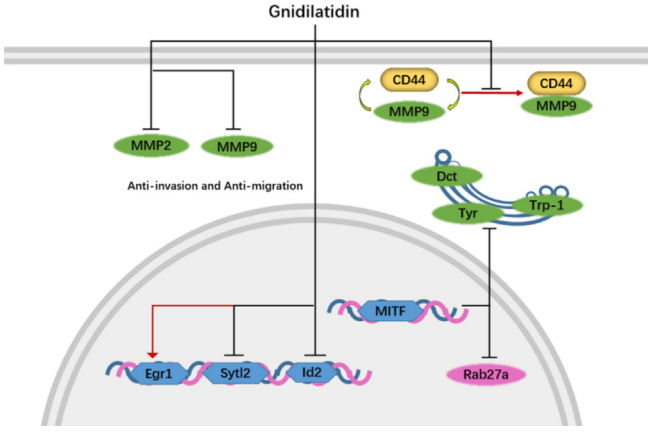


Fig. 12. Molecular mechanisms of Daphnane-type diterpenes on melanoma.

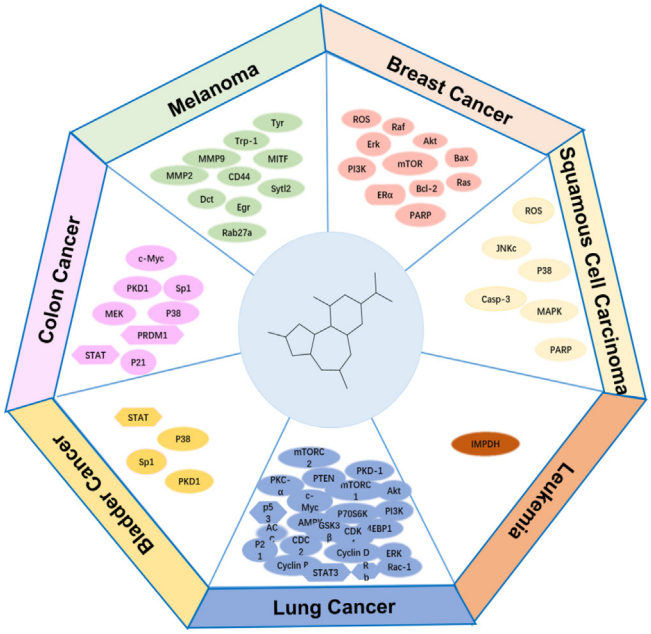


Fig. 13. Molecular mechanisms of Daphnane-type diterpenes on cancer.

them show different degrees of inhibitory effect on various cancer cells and we have mapped their pharmacological mechanism of action.

An appealing opportunity is raised by the repeated that although there are 95 species of this genus, relatively few reports of this type of compounds. No doubt that here still a promising research about the genus. Unfortunately, an appealing question is also occurring that most of the current research on the activity of these compounds is focused on simple drug efficacy (~29%), and its in-depth mechanism research (~10%) is far from enough (Fig. 15).

We thought that the production of natural product may be the mainly barrier of its application to a certain extent. Maybe, we can try to solve this problem in a synthetic way. This raised the prospect of promoting a further research of these compounds based on the expected activity. In addition, most of this type of compound contains toxicity which may also be the limiting. We can try to modify its structure based on the related research on its structure–activity relationship in order to maximize its application. Furthermore, the combination of drugs may also be an effective way to reduce its toxicity

Development of effective drugs is the holy grail of researchers. However, drug development faces multiple challenges that lead high costs and long development cycles for new therapeutics. In this condition, natural medicine with multiple targets, relatively low resistance has attracted the attention of researchers. Like a river flows, surely to the sea. Therefore, we summarize the current research status, in order to find a suitable breakthrough for further development and utilization of this type of compound. Hopping call for more researchers putting emphasis on its derivatives, pharmacology, toxicology and pharmacokinetic research.

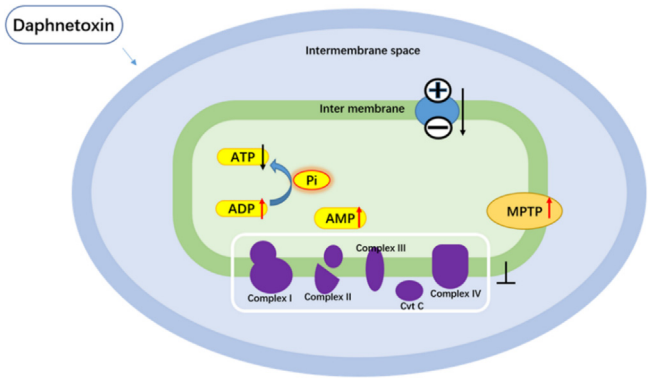


Fig. 14. Molecular mechanisms of Daphnane-type diterpenes on mitochondrial.

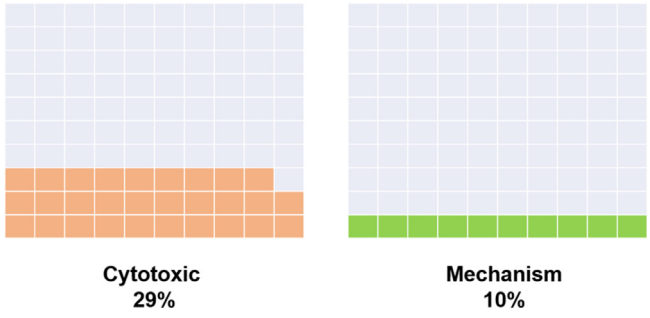


Fig. 15. Current status of activity research of Daphnane-type diterpenes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chmed.2020.09.006.

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