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REVIEW

Targeting cancer with sesterterpenoids: the new potential antitumor drugs

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Abstract Cancer remains a major cause of death in the world to date. A variety of anticancer drugs have been used in clinical chemotherapy, acting on the particular oncogenic abnormalities that are responsible for malignant transformation and progression. Interestingly, some of these anticancer drugs are developed from natural sources such as plants, marine organisms, and microorganisms. Over the past decades, a family of naturally occuring molecules, namely sesterterpenoids, has been isolated from different organisms and they exhibit significant potential in the inhibition of tumor cells in vitro, while the molecular targets of these compounds and their functional mechanisms are still obscure. In this review, we summarize and discuss the functions of these sesterterpenoids in the inhibition of cancer cells. Moreover, we also highlight and discuss chemical structure–activity relationships of some compounds, demonstrating their pervasiveness and importance in cancer therapy.

Keywords Terpenoids · Sesterterpenoids · Cancer therapy · Structure–activity relationship

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Introduction: overview of sesterterpenoids and their biological functions

Natural compounds sourced from different organisms exhibit immense structural diversity and possess extensively biological activities against malaria, inflammation, multiple types of cancer, and many infectious diseases. Many of these compounds have been used in clinical therapy, such as etoposide [1], vincristine [2], irinotecan [3], and paclitaxel [4]. As the largest subclass of natural products, accounting for more than 40,000 individual compounds, terpenoids also exhibit diverse biological functions, particularly in the prevention and therapy of multiple cancer types such as skin, lung, pancreatic, colon, and prostate cancer [5, 6]. Based on the number of isoprene units building their parent terpene scaffold, terpenoids can be generally categorized into hemiterpenoids (C_5), monoterpenoids (C_{10}), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), sesterterpenoids (C_{25}), triterpenoids (C_{30}), tetraterpenoids (C_{40}), and polyterpenoids (more than C_{40}) [7, 8]. Among these terpenoids, pharmaceutical effects against tumor cells have been extensively reported in monoterpenoids and triterpenoids [9–11], which exhibit the ability to suppress the growth of cancer cells by inducing tumor cell differentiation and apoptosis, and inhibiting tumor angiogenesis, invasion, and metastasis [12–14]. In recent years, sesterterpenoids, a small subgroup of terpenoids, have been widely isolated from different organisms, and also exhibit diverse biological properties involving anti-inflammatory, antimicrobial, anti-feedant, antitubercular, and anti-biofilm formation [7, 8]. Some sesterterpenoids even possess multifunctional activities. For instance, manoalide has both anti-inflammatory and antimicrobial activities [7, 8]. Importantly, many sesterterpenoids can suppress the growth of cancer cells in vitro, and are therefore considered as

promising candidates for anticancer drugs [7, 8, 15]. However, their functional mechanisms and molecular targets are barely known to date.

Sesterterpenoids commonly harbor C_{25} carbon skeletons in their molecular structures. However, some compounds that contain C_{21}–C_{24} are also grouped into sesterterpenoids, termed as norsesterterpenoids [7, 8]. So far, nearly 1,000 sesterterpenoids have been isolated from terrestrial fungi, lichens, higher plants, insects, and various marine organisms, particularly sponges [8, 16]. Based on the carbocycle numbers contained in their molecular structures, sesterterpenoids can be broadly classified into 6 subgroups: linear, monocarbocyclic, bicarbocyclic, tricarbocyclic, tetracarbocyclic, and miscellaneous sesterterpenoids [7, 8, 17]. All of these six subclasses of sesterterpenoids have been reported to exhibit significant cytotoxicities against tumor cells.

Linear sesterterpenoids and their cytotoxicities against tumor cells

Although the structures of linear sesterterpenoids are very simple, many of them possess significant cytotoxicities against human tumor cells, with unknown mechanisms of action. Four C_{22} furanosesterterpenoids isolated from the *Ircinia* species of sponges, including ircinformonins C (**1**), D (**2**), 15-acetylircinformonin B (**3**), and 10-acetylircinformonin B (**4**) [18], have been reported to significantly inhibit different human cancer cells, in which compounds (**1**) and (**2**) suppress the growth of colon tumor cells, and compounds (**3**) and (**4**) display notable cytotoxic activities against K562, DLD-1, HepG2, and Hep3B cancer cells [8, 19]. Some haslenes (**5**–**7**) (from *Haslea ostrearia*) that house C25 highly branched isoprenoid (HBI) alkenes appear to possess cytostatic effects on human lung cancer cells in vitro [20, 21]. Four furanosesterterpenes isolated from the marine sponge *Ircinia oros*, ircinin-1 (**8**) [22], (7*E*, 12*E*, 18*R*, 20*Z*)-variabilin (**9**) [23], (8*E*, 13*Z*, 18*R*, 20*Z*)-strobilinin (**10**) [23], and (7*E*, 13*Z*, 18*R*, 20*Z*)-felixinin (**11**) [23], have been demonstrated to show cytotoxicities against SK–MEL-2 human cancer cells by inducing cell cycle arrest and apoptosis [8, 22]. Supplementation with ircinin-1 (**8**) can lead to G1 phase arrest during cell cycle progression, and this process is associated with a marked decrease in protein levels of cyclin D, CDK4 and CDK6 [22]. Ircinin-1 can also induce the release of cytochrome *c*, activation of caspase-3 and caspase-9, and upregulation of Fas and Fas-L [22].

Moreover, furospinosulin-1 (**12**), a marine-sponge-derived furanosesterterpene, exhibits activity against DU145 human prostate cancer cells by inhibiting cell proliferation [24]. Subsequent study has demonstrated that furospinosulin-1 could suppress the expression of insulin-like growth factor-2 (IGF-2) [24], which is a hypoxia-inducible angiogenic factor and is selectively induced under hypoxic conditions through inhibiting the binding of nuclear proteins to the Sp1 consensus sequence in the IGF-2 promoter region [24] (Fig. 1).

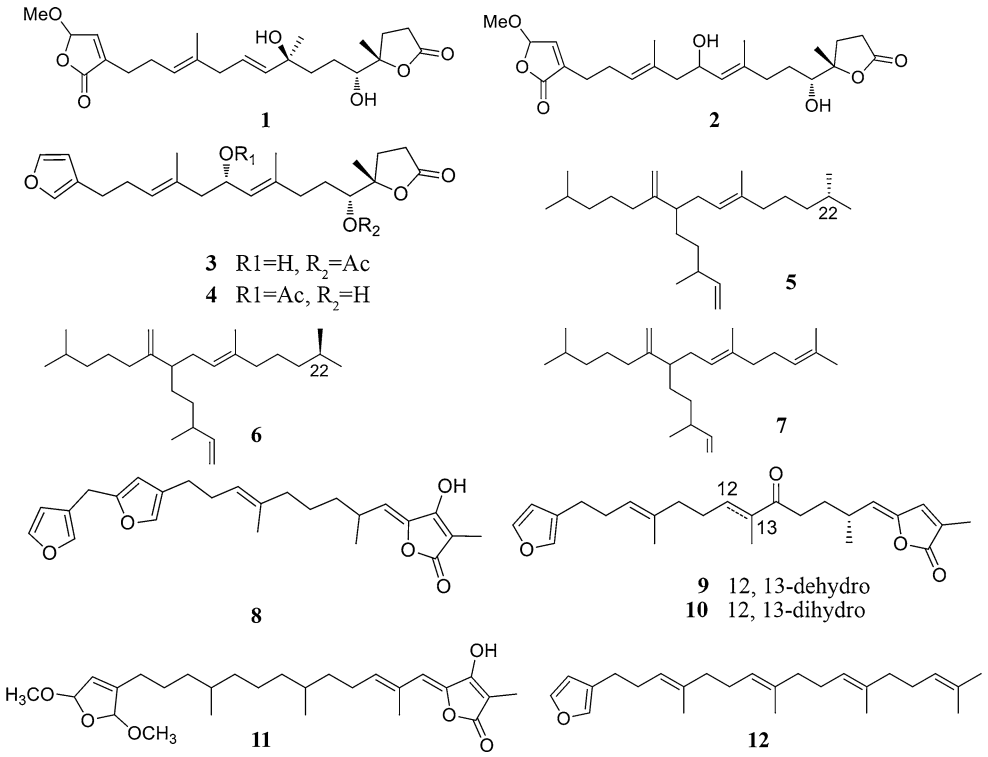

Fig. 1 Structures of linear sesterterpenoids **1**–**12**

Monobocyclic sesterterpenoids and their cytotoxicities against tumor cells

A variety of monobocyclic sesterterpenoid compounds have also been demonstrated to exhibit significant cytotoxicities. However, little is known about their functional mechanisms. 24-*n*-Propyl-*O*-manoalide (**13**), a derivative of manoalide, was isolated from *Luffariella* species [25] and showed significant cytotoxicity against HCT-116 cancer cells [25]. Some monobocyclic sesterterpenoids isolated from *Diacarnus cf. spinopoculum*, including *ent*-muqubilin A (**14**), *ent*-epimuqubilin A (**15**), nuapapuin B (**16**), *epi*-nuapapuin B (**17**), muqubilin B (**18**), and *epi*-muqubilin B (**19**), possess cytotoxicities against NCI-60 cells [8, 26]. The diacarnoxides A (**20**) and B (**21**), isolated from *Diacarnus levii*, display cytotoxicities against T47D breast tumor cells by inhibiting HIF-1 (hypoxia-inducible factor) activation under hypoxic conditions [27]. It should be noticed here that the activity of HIF-1 is involved in angiogenesis required for tumor cell growth, and thus HIF-1 inhibitors are now under investigation for anticancer effects [28]. The aplysinoplides A–C (**22–24**) identified in *Aplysinopsis digitata* have cytotoxicities against P-388 mouse leukemia cells [29]. Luffariolides A–J (**25–33**), obtained from *Luffariella* species of marine sponge, exhibit significant cytotoxicities against murine lymphoma L1210 cells. Of them, luffariolides A (**25**), B (**26**), E (**29**), and F (**30**) show the most significant activities [15, 30, 31] (Fig. 2).

Bicarbocyclic sesterterpenoids and their cytotoxicities against tumor cells

Sesterterpenoids with a bicarbocyclic skeleton in many compounds show structures reminiscent of the clerodane and labdane diterpenoids [7, 8]. Kohamaic acid A (**34**) [32], a compound isolated from *Ircinia* species of marine sponge, functions as a powerful inhibitor of DNA

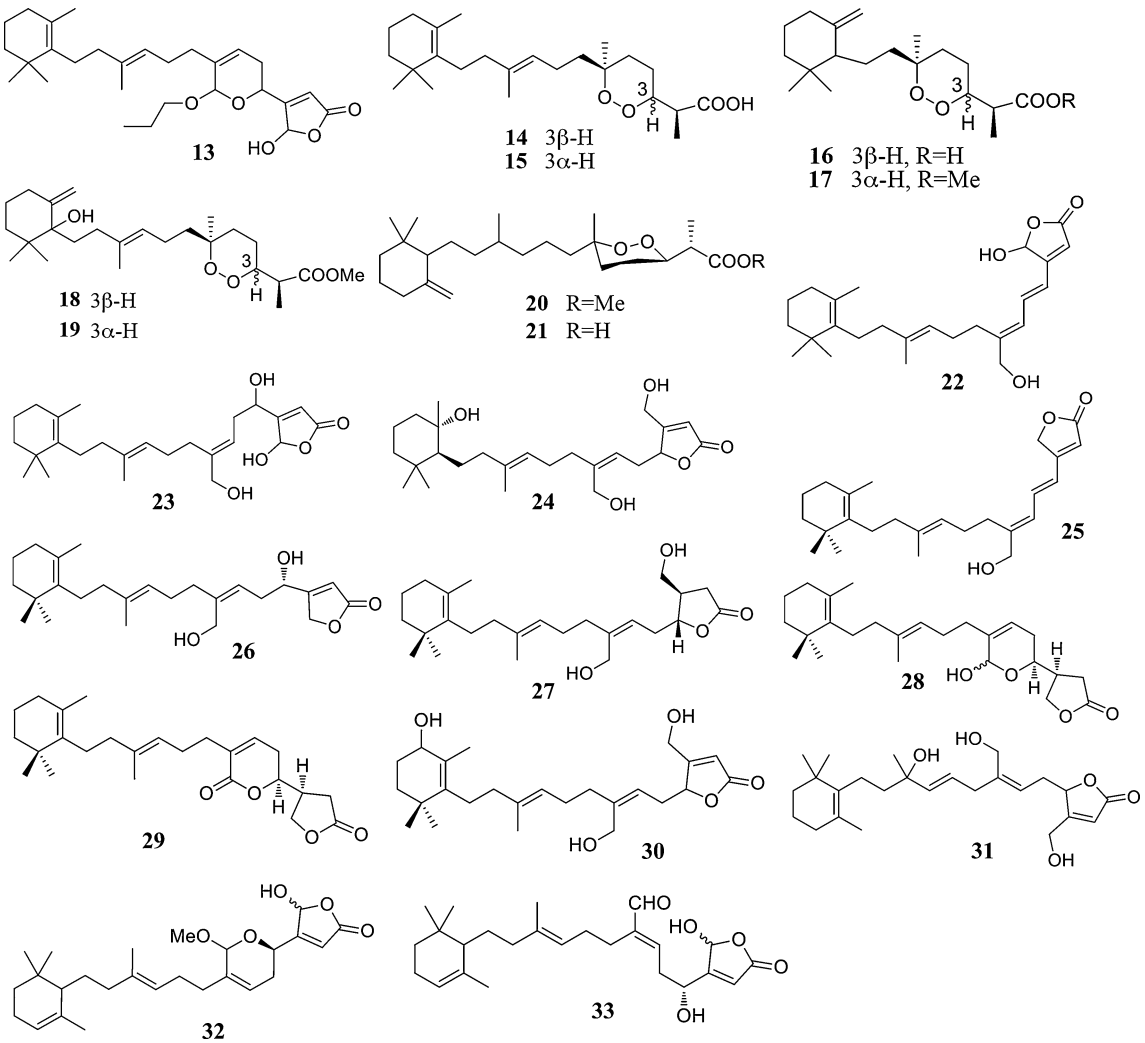

Fig. 2 Structures of monobocyclic sesterterpenoids **13–33**

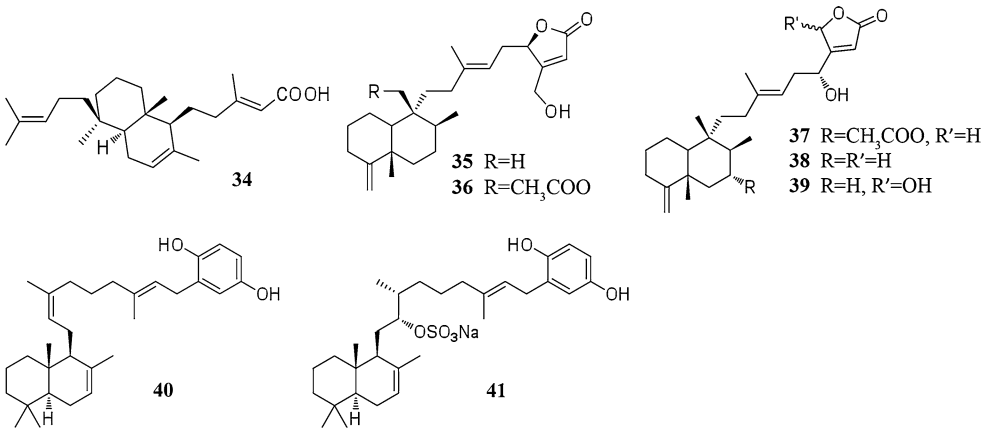

Fig. 3 Structures of bicarbocyclic sesterterpenoids **34–41**

polymerases [32], which are specialized for DNA replication and repair, and can help cancer cells tolerate DNA damage [33]. Some of these enzymes have been developed as viable targets for therapeutic strategies of cancer [33]. The derivatives of kohamaic acid A have also been shown to prevent the growth of HL-60 human cancer cells through inhibition of DNA replication and repair processes [34]. Several sesterterpenes, including thorectandrols A–D (**35–38**) [35, 36] and palauolol (**39**) [37], share similar chemical structures and also display cytotoxicities against a variety of cancer cell lines [38]. Palauolol shows significant inhibitory activity against MCF-7, SNB-19, COLO-205, KM12, MOLT-4, H460, A549, LOX, and MALME-3 tumor cell lines, whereas thorectandrols A–D only display weak activities against some of them [38]. Two other sesterterpenoids (**40** and **41**), which were isolated from the *Coscinoderma* species of sponge, exhibit moderate cytotoxicities against K562 cells [39] (Fig. 3).

Tricarbocyclic sesterterpenoids and their cytotoxicities against tumor cells

Many sesterterpenoids that possess tricarbocyclic skeleton have also been found to show cytotoxicities. Ophiobolins, including ophiobolin A (**42**), 6-*epi*-ophiobolin A (**43**), 3-anhydro-6-*epi*-ophiobolin A (**44**), and ophiobolin I (**45**), were isolated from *Bipolaris* species [40]. All of them have cytotoxic activities against A-549, HT-29, and Mec-20 human tumor cells [40]. Mechanistic analysis indicates that ophiobolin A suppresses proliferation and migration of cancer cells, and it triggers a paraptosis-like cell death through disrupting internal potassium ion homeostasis [41]. Both **43** and **44** exhibit significant cytotoxicities, whereas ophiobolin I only shows weak activity against tumor cells in comparison with compound **43** [7].

Aurorals (**46–47**) isolated from the sponge *Rhabdastrella globostellata* were found to exhibit cytotoxicities against KB cells [42]. Seven sesterterpenoids isolated from *Petrosaspongia nigra*, namely petrosaspongiolides C–H (**50–55**) and L (**56**), exhibit cytotoxicities against NSCLC-N6 human bronchopulmunary non-small-cell-lung carcinoma cells [43]. The scalarane-related sesterterpene hyatolides A (**57**) identified in the sponge *Hyatella intestinalis* has shown activity as a growth inhibitor of several tumor cell lines such as MDA-MB-231, A-549, and HT-29 [44]. Five isomalabaricane-derived natural products from *Rhabdastrella globostellata*, namely globostelletins C–G (**58–62**), display different activities against human tumor cell lines such as A549, BGC-823, HCT-8, Bel-7402, and A2780 [45]. A globostelletin-derived compound, namely rhabdastrellic acid A (**63**), has been shown to have potent inhibition against HL-60 cells by inducing apoptosis in M/G2 phase [46]. Further studies indicate that rhabdastrellic acid A can inhibit proliferation of Hep3B and A549 tumor cells and induce autophagy-associated cell death through blocking the Akt pathway [46]. This process can be negated by transfection with constitutively active Akt plasmid [46] (Fig. 4).

Tetracarbocyclic sesterterpenoids and their cytotoxicities against tumor cells

Tetracarbocyclic sesterterpenoids are emerging as a class of attractive compounds exhibiting significant activities against tumor cells. Scalaranes, the most common sesterterpenoids, have been reported to possess broad and significant cytotoxicities against cancer cells [47]. Among them, three scalaranes isolated from *Haloragis erecta*, namely salmahyrtisol B (**64**), 3-acetyl- and 19-acetyl-sesterstatin (**65** and **66**), show significant cytotoxicities against P-388, A-549, and HT-29 tumor cells [47]. A pentacyclic sesterterpene isolated from *Haloragis erecta*, namely sesterstatin 6 (**67**), shows significant cytotoxicity against murine leukemia (P-388) and some human tumor cell lines, including BXPC-3, KAT-4, SW1736, NCI-H460, FADU,

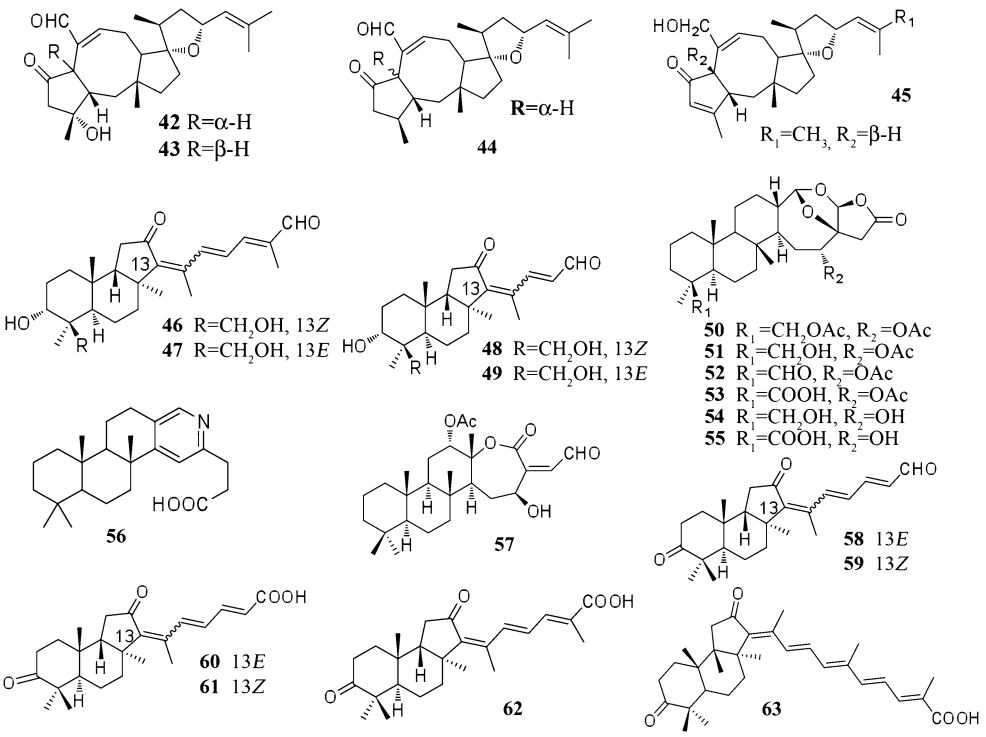

Fig. 4 Structures of tricarbocyclic sesterterpenoids **42–63**

and DU-145 [48]. Hyatelactam (**68**), isolated from *Hyatella intestinalis*, has been shown to inhibit HT-29 tumor cells [44]. Hippospongide B (**69**), which was isolated from a *Hippospongia* species of sponge, exhibits significant cytotoxicity against DLD-1, HCT-116, T-47D, and K562 tumor cells [49]. Seven other novel scalarane sesterterpenes isolated from *Psammocinia* species, namely 12-deacetoxy-23-hydroxyscalaradial (**70**), 12-deacetoxyscalaradial (**71**), 12-dehydroxy-23-hydroxyhyrtiolide (**72**), 12-*O*-acetyl-16-deacetoxy-23-acetoxyscalarafuran (**73**), 12-deacetoxy-23-hydroxyheteronemin (**74**), 12-deacetoxy-23-*O*-acetoxyheteronemin (**75**), and 12-deacetoxy-23-acetoxy-19-*O*-acetylscalarin (**76**), exhibit cytotoxicities against human renal cancer cell lines (A498, ACHN), pancreatic cancer cell lines (MIA-paca, PANC-1), and noncancerous monkey cell line (CV-1) in vitro [50].

Hyatelone A (**77**), 19,20-di-*O*-acetylhyatelone B (**78**), and 20-*O*-acetylhyatolide C (**79**) posses cytotoxicities against MDA-MB-231, A-549, and HT-29 tumor cells [44]. Beside anti-feedant and anti-inflammatory properties, scalarenedial (**80**) also displays cytotoxicity against HL-60 cells [51]. 12-*O*-Deacetylnorscalaral B (**81**), isolated from the sponge *Hyatella intestinalis*, exhibits activity to inhibit the growth of MDA-MB-231, A-549, and HT-29 tumor cells [44]. Sesterterpene polyols, the mangicols A–G (**82–88**), which possess unprecedented spirotricyclic skeletal components, show only weak-to-modest cytotoxicities against a variety of cancer cell lines in vitro, especially for NCI-60 cells [52]. Heteronemin (**89**), a spongean sesterterpenoid isolated from *Hyrtios* species, inhibits TNFα-induced NF-κB (nuclear factor kappa-B) activation through proteasome inhibition and induces apoptotic cell death [53, 54]. Heteronemin can affect a variety of cellular processes including cell cycle, apoptosis, the mitogen-activated protein kinases (MAPKs) pathway and the NF-κB signaling cascade, thereby contributing to tumor cell growth inhibition [53, 54]. PHC-2–PHC-7 (**90–95**), which were isolated from *Phyllospongia chondrodes*, can increase hemoglobin production in human chronic myelogenous leukemia cell line K562 by inducing erythroid differentiation [55]. Neomangicols A (**96**) and B (**97**) are cytotoxic to HCT-116 human colon carcinoma in vitro [56].

Moreover, scalaradial (**80**) and cacospongionolide A (**98**) should be particularly noted; they are isolated from *Cacospongia scalaris* and *Fasciospongia cavernosa* marine sponges, respectively, and can significantly inhibit the growth of T47D, A431, HeLa, and HCT116 cells with different mechanisms [57]. Detailed studies indicate that treatment of T47D cells with scalaradial or cacospongionolide can lead to increased DNA migration and fragmentation [57]. Incubation of HCT116 and HeLa cells with scalaradial or cacospongionolide results in increased pro-apoptotic protein levels and the loss of mitochondrial transmembrane [57], implying the activation of apoptosis signaling. These results suggest that scalaradial and cacospongionolide may represent new promising compounds for inhibiting cancer cell proliferation (Fig. 5).

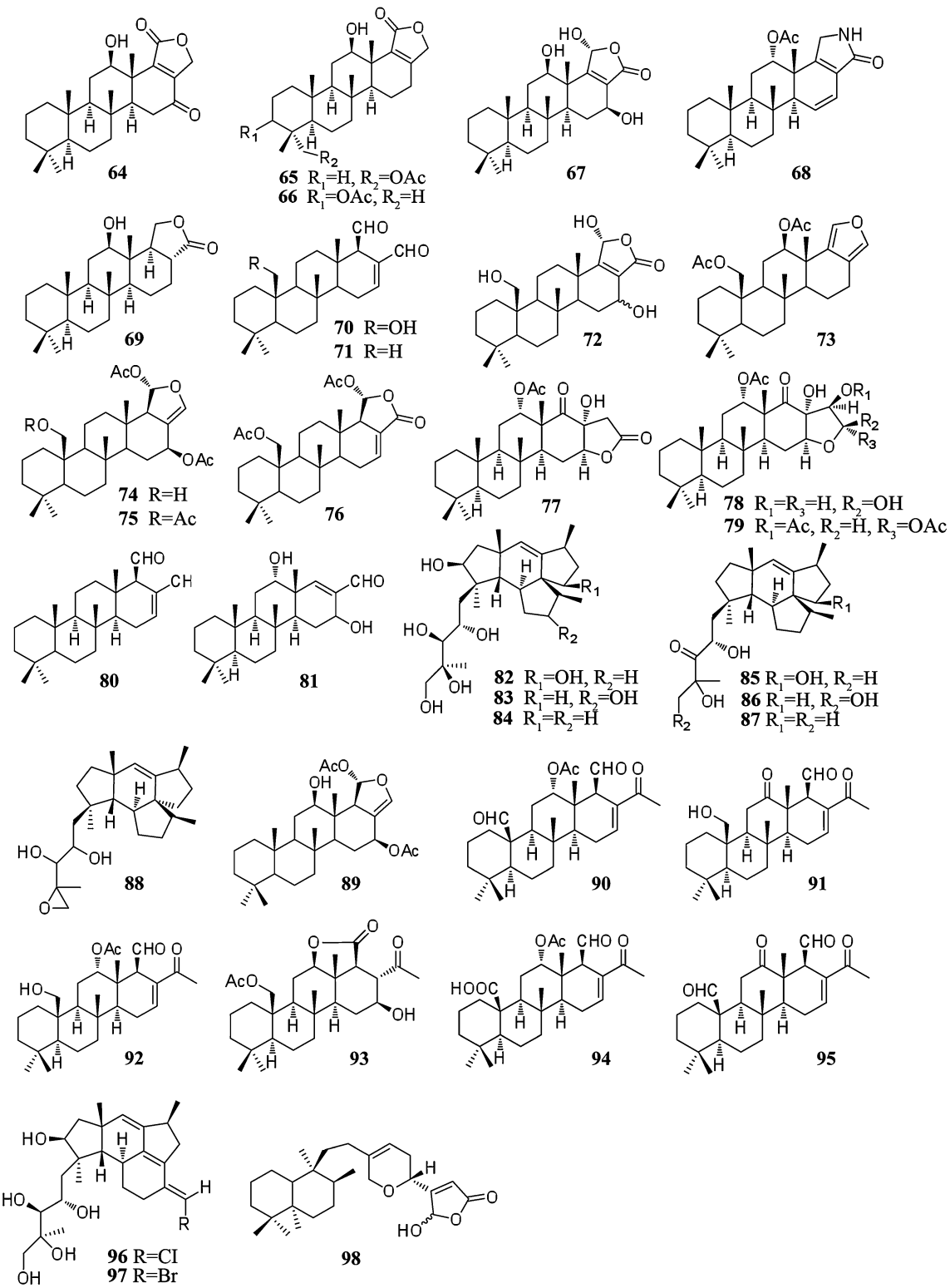

Fig. 5 Structures of tetracarbocyclic sesterterpenoids **64–98**

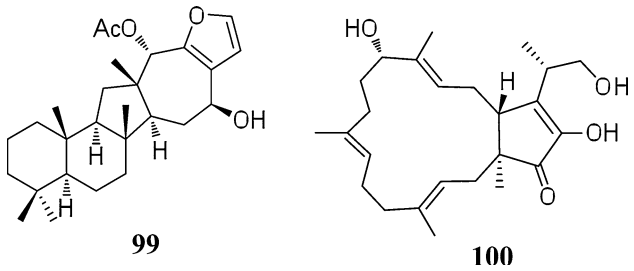

Fig. 6 Structures of miscellaneous sesterterpenoids **99**–**100**

Miscellaneous sesterterpenoids and their cytotoxicities against tumor cells

Studies also demonstrate that miscellaneous sesterterpenoids exhibit significant cytotoxicities against tumor cells. Salmahyrtisol A (**99**), which was isolated from *Hyrtios erecta*, exhibits significant cytotoxicity against murine leukemia (P-388), A-549, and HT-29 human cancer cells [58]. Terpestacin (**100**), a miscellaneous compound, was isolated from a *Phomopsis* species of fungus [59]. Mechanistic study indicates that terpestacin suppresses tumor angiogenesis by targeting UQCRB of mitochondrial complex III in the mitochondrial respiratory chain, thereby causing the inhibition of hypoxia-induced reactive oxygen species and cellular oxygen sensing [59, 60] (Fig. 6).

Chemical structure–activity relationships

Some sesterterpenes share similar chemical structures but exhibit distinct cytotoxic activities against cancer cells. Thus, it will be interesting and helpful to investigate the relationship between chemical structure and activity. Although many sesterterpenes have been found to show cytotoxicities to tumor cells, it is impossible to compare their activities meaningfully since different cancer cell lines were used for different compounds in cytotoxic assays. Here, we track some sesterterpenes isolated by Dr. Liu's group (from South China Sea Institute of Oceanology) in the past years, and try to find factors affecting their activities (Table 1), thereby providing guidance for modifying the chemical structure of sesterterpenes and obtaining derivatives with more bioactivity in the future.

C-21 structures and cytotoxicities against tumor cells

Sarcotin A, a compound isolated from *Sarcotragus* species, possesses a pair of epimers, C-21*R* (**101**) and *C*-21*S* (**102**) [61]. Cytotoxicity analysis indicates that the C-21*R* epimer is much more cytotoxic than the C-21*S* epimer. Consistent with this, sarcotin B (**103**) and isopalinurin (**104**), and the other two furanosesterterpenes (**105** and **106**) from *Psammocinia* species also show much higher cytotoxicity to cancer cells in their C-21*R* epimers than their respective C-21*S* epimers [62] (Fig. 7)

γ-Hydroxybutenolide moiety and cytotoxicities against tumor cells

Some cacospongionolides (**98**, **107**–**108**) share similar chemical structures with thorectandrols, but exhibit significantly higher cytotoxicities than thorectandrols. Their structure comparison suggests a possible relationship between the γ-hydroxybutenolide moiety and cytotoxicity [57, 63]. Furthermore, some sesterterpenes including a norsesterterpenoid compound (**109**), sarcotin I (**110**) and sarcotin J (**111**) [61, 64], share similar chemical structures with compound **101**. However, their cytotoxicities against cancer cells are weaker than compound **101**, which contains a γ-hydroxybutenolide moiety. These results clearly demonstrate that the γ-hydroxybutenolide moiety is necessary for the activities of sesterterpenes, and the opening ring of γ-hydroxybutenolide may also cause the decrease in cytotoxicity (Fig. 8).

Furan moiety and cytotoxicities against tumor cells

The furan moiety also displays a relevance to cytotoxicity. Comparison of the chemical structures and cytotoxicities of compounds **109** and **112**–**113** indicates that sesterterpenes containing a furan moiety have increased cytotoxicity when the furan moiety is oxygenated to form unsaturated lactone or dihydrofuran [63, 64]. Moreover, sesterterpenes **8** and **114**–**117** containing two furan moieties show higher cytotoxicities than those compounds (**118**–**120**) that contain only one furan moiety [65]. That is to say, the more furan rings means stronger cytotoxicities, and the oxidation of a furan ring at an appropriate degree might also improve the cytotoxicities of sesterterpenes (Fig. 9).

Pyrrole moiety and cytotoxicities against tumor cells

The pyrrolosesterterpenes are chemically unique compounds, and incorporate a pyrrole ring to replace the furan ring. The pyrrole moiety also displays correlation with cytotoxicity in sesterterpenes. Comparison of the chemical structures and activities of compound **118** and sesterterpenes **121**–**126** indicates increased cytotoxicity in compounds harboring a pyrrole moiety [61]. However, sesterterpenes carrying a β-substituted lactam ring (**127**) instead of the α-substituted one exhibit dramatically decreased activity [61]. Moreover, an alkyl moiety attached

Table 1 Cytotoxic activities of compounds

Compound	Tumor cell lines					Reference
	A549	SK-MEL-2	SK-OV-3	HCT15	XF498	
101	29.7	>30	22.1	27.2	24.8	[61]
102	12.3	5.6	9.6	6.5	9.8	[61]
103	10.1	7.8	11.3	9.0	8.9	[61]
104	5.2	4.4	10.2	5.4	5.1	[61]
105	>30	10.7	16.5	>30	10.0	[62]
106	24.1	19.0	18.6	23.5	22.1	[62]
109	19.4	10.9	>30	21.7	>30	[61, 64]
110	24.8	25.7	23.3	23.7	25.9	[61, 64]
111	18.1	7.8	10.0	8.7	24.3	[61, 64]
112	24.1	15.2	7.6	10.5	20.1	[61, 65]
113	8.2	7.5	12.6	19.2	7.8	[61, 65]
114	3.7	9.0	6.6	6.9	5.4	[61, 65]
115	5.0	10.2	9.4	9.8	6.5	[61, 65]
116	3.8	5.9	5.9	4.7	3.7	[61, 65]
117	3.8	8.4	6.2	7.3	5.0	[61, 65]
118	29.7	>30	22.1	27.2	24.8	[61, 65]
119	10.1	7.8	11.3	9.0	9.0	[61, 65]
120	16.89	16.3	26.8	27.5	20.4	[61, 65]
121	15.1	4.1	5.3	5.0	5.5	[61]
122	4.3	3.4	4.0	3.8	3.9	[61]
123	6.3	4.3	6.7	4.9	5.2	[61]
124	16.8	4.8	13.1	5.4	10.5	[61]
125	19.0	3.8	6.9	5.3	5.4	[61]
126	27.1	15.9	26.8	22.3	25.2	[61]
127	>30	13.2	25.9	21.6	>30	[61]
128	>30	10.9	>30	33.0	>30	[64]
129	>30	>30	>30	>30	>30	[64]
130	>30	>30	>30	>30	>30	[64]
131	>30	>30	>30	>30	>30	[64]
9	>30	7.5	>30	20.5	28.1	[60]
10	7.5	12.3	4.8	11.7	10.5	[60]

Data expressed as ED_{50} values (μg/mL)

A549 human lung cancer cell line, *SK-MEL-2* human skin cancer cancer cell line, *SK-OV-3* human ovarian cancer cell line, *HCT15* human colon cancer cell line, *XF498* human CNS cancer cell line

on the N-atom of the pyrrole ring is also required for cytotoxicity. For instance, some sesterterpenes (**128–131**), in which the alkyl moieties are substituted by carboxylic acid sodium, show completely absent cytotoxicity [64] (Fig. 10).

Double bonds and cytotoxicities against tumor cells

The double bonds within the sesterterpenes also have significant effects on cytotoxicity, and the effect is complicated. For instance, comparison of cytotoxicities of two furanosesterterpenes (**9** and **10**) isolated from a *Psammocinia* species of marine sponge [60] clearly indicates that compound **10** which carries a double bond in $\Delta^{12,13}$ has much higher cytotoxicity than **9** [60]. Furthermore, the configuration of double bonds also plays important roles for the activities of compounds. Some *E*-difuranosesterterpenes (**115** and **117**) have been reported to display lower activities than their respective *Z*-difuranosesterterpenes (**114** and **116**) [65]. The different position of double bonds may lead to different activities. For instance, compounds **105** and **106** share similar structures, but have different positions of double bonds. Interestingly, compound **105** exhibits higher cytotoxicity than **106** in SK-MEL-2, SK-OV-3, and XF498

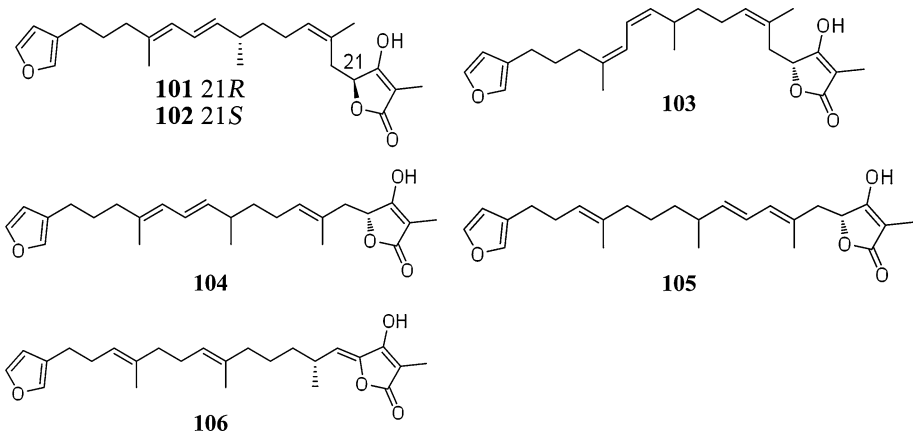

Fig. 7 Structures of C-21-containing sesterterpenoids **101–106**

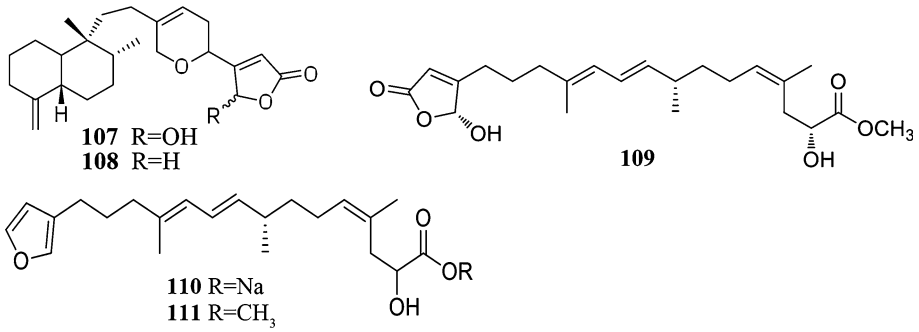

Fig. 8 Structures of γ-hydroxybutenolide moiety-containing sesterterpenoids **107–111**

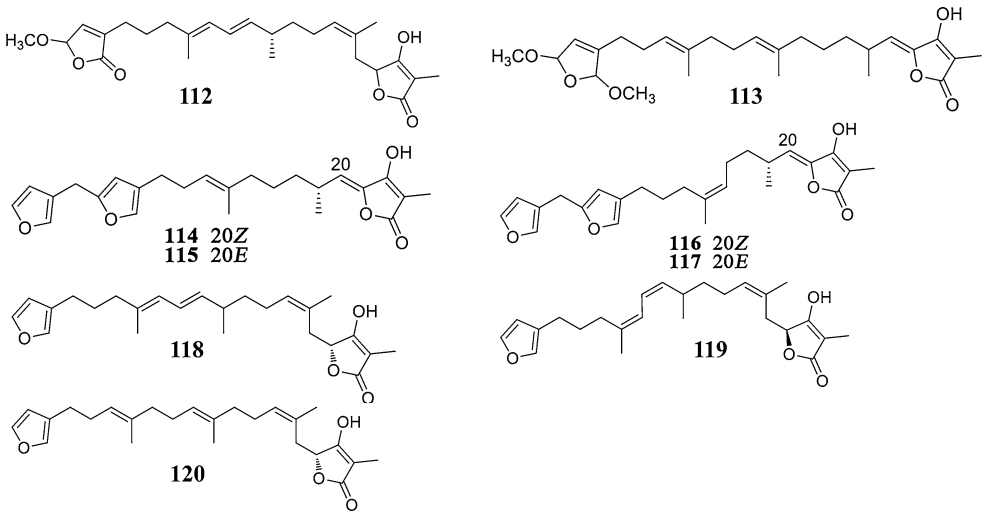

Fig. 9 Structures of furan moiety-containing sesterterpenoids **112–120**

tumor cells [62]. These results indicate that the $\Delta^{8(10),11(12)}$ conjugated double bonds may increase cytotoxicity, whereas the $\Delta^{15(16),17(18)}$ double bonds possibly decrease activity. Taken together, the characteristics of double bonds including number, position and configuration show significant effects on the cytotoxicity of sesterterpenes.

Challenges and future directions

One challenge for cancer chemotherapy is the lack of effective antitumor drugs. The traditional chemotherapeutic medicines cannot selectively kill cancer cells, and consequently cause serious side effects including immuno-

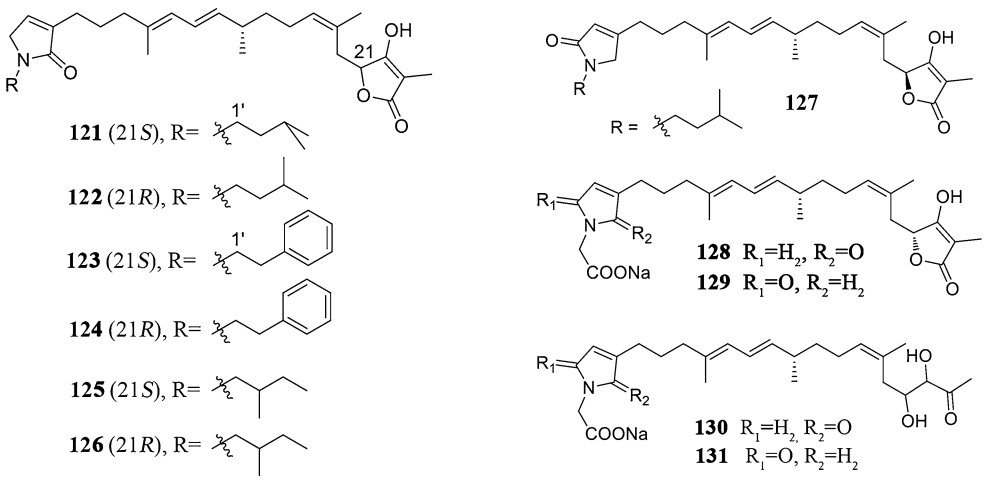

Fig. 10 Structures of pyrrole moiety-containing sesterterpenoids **121–131**

logical, neurological, metabolic, and infectious diseases. Developing compounds from natural sourcea as anticancer drugs is a new strategy to overcome or decrease these side effects. Interestingly, many sesterterpenoids from natural sources have been reported to exhibit strong cytotoxicities by inhibiting cancer cell proliferation and/or inducing cell death. These sesterterpenoids are attracting more interest and may represent new promising compounds in cancer therapy.

Although many sesterterpenoids have been reported to exhibit significant cytotoxicities in vitro, few studies have provided insights into their molecular targets and mechanisms. Thus, it is necessary to further explore studies on signal transduction involved in cancer pathways, the in vivo physiological roles and the systematic structure–activity relationships of these compounds. The detailed mechanistic understanding of sesterterpenoids may provide critical insights into future development and investigation of cancer therapeutics with higher specificity and selectivity. The commendable understanding of relationship between structures and activities can, in turn, help us to chemically modify and synthesize powerful compounds against tumor cells. Furthermore, we anticipate establishing a sesterterpenoid compound-bank to screen effective and specific compounds against various diseases, including but not limited to cancer. Sesterterpenoids may be used in combination with other chemotherapeutic drugs to increase effectiveness and decrease doses of individual compounds, therefore reducing side effects.

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References

1. Hande KR (1998) Etoposide: four decades of development of a topoisomerase II inhibitor. Eur J Cancer 34:1514–1521
2. Boslooper K, Kibbelaar R, Storm H, Veeger NJ, Hovenga S, Woolthuis G, van Rees B, de Graaf E, van Roon E, Kluin-Nelemans HC (2014) Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone is beneficial but toxic in very elderly patients with diffuse large B-cell lymphoma: a population-based cohort study on treatment, toxicity and outcome. Leuk Lymphoma 55:526–532
3. Morland B, Platt K, Whelan JS (2014) A phase II window study of irinotecan (CPT-11) in high risk Ewing sarcoma: a Euro-E.W.I.N.G. study. Pediatr Blood Cancer 61:442–445
4. Cui L, Liu XX, Jiang Y, Liu JJ, Zhou XR, He XJ, Chen J, Huang XE (2014) Phase II study on dose escalating schedule of paclitaxel concurrent with radiotherapy in treating patients with locally advanced non-small cell lung cancer. Asian Pac J Cancer Prev 15:1699–1702
5. Gershenzon J, Dudareva N (2007) The function of terpene natural products in the natural world. Nat Chem Biol 3:408–414
6. Degenhardt J, Kollner TG, Gershenzon J (2009) Monoterpene and sesquiterpene synthases and the origin of terpene skeletal diversity in plants. Phytochemistry 70:1621–1637
7. Liu Y, Wang L, Jung JH, Zhang S (2007) Sesterterpenoids. Nat Prod Rep 24:1401–1429
8. Wang L, Yang B, Lin XP, Zhou XF, Liu Y (2013) Sesterterpenoids. Nat Prod Rep 2013(30):455–473
9. Huang M, Lu JJ, Huang MQ, Bao JL, Chen XP, Wang YT (2012) Terpenoids: natural products for cancer therapy. Expert Opin Investig Drugs 21:1801–1818
10. Rabi T, Bishayee A (2009) Terpenoids and breast cancer chemoprevention. Breast Cancer Res Treat 115:223–239
11. Thoppil RJ, Bishayee A (2011) Terpenoids as potential chemopreventive and therapeutic agents in liver cancer. World J Hepatol 3:228–249
12. Sagar SM, Yance D, Wong RK (2006) Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer - Part 1. Curr Oncol 13:14–26
13. Kuttan G, Pratheeshkumar P, Manu KA, Kuttan R (2011) Inhibition of tumor progression by naturally occurring terpenoids. Pharm Biol 49:995–1007
14. Yang H, Dou QP (2010) Targeting apoptosis pathway with natural terpenoids: implications for treatment of breast and prostate cancer. Curr Drug Targets 11:733–744

15. Ebada SS, Lin W, Proksch P (2010) Bioactive sesterterpenes and triterpenes from marine sponges: occurrence and pharmacological significance. Mar Drugs 8:313–346
16. Li GY, Li BG, Yang T, Yin JH, Qi HY, Liu GY, Zhang GL (2005) Sesterterpenoids, terretonins A-D, and an alkaloid, asterrelenin, from *Aspergillus terreus*. J Nat Prod 68:1243–1246
17. Hog DT, Webster R, Trauner D (2012) Synthetic approaches toward sesterterpenoids. Nat Prod Rep 29:752–779
18. Shen YC, Liaw CC, Ho JR, Khalil AT, Kuo YH (2006) Isolation of aureol from *Smenospongia* sp. and cytotoxic activity of some aureol derivatives. Nat Prod Res 20:578–585
19. Su JH, Tseng SW, Lu MC, Liu LL, Chou Y, Sung PJ (2011) Cytotoxic C21 and C22 terpenoid-derived metabolites from the sponge *Ircinia* sp. J Nat Prod 74:2005–2009
20. Rowland SJ, Belt ST, Wraige EJ, Masse G, Roussakis C, Robert JM (2001) Effects of temperature on polyunsaturation in cytostatic lipids of *Haslea ostrearia*. Phytochemistry 56:597–602
21. Allard WG, Belt ST, Masse G, Naumann R, Robert JM, Rowland S (2001) Tetra-unsaturated sesterterpenoids (Haslenes) from *Haslea ostrearia* and related species. Phytochemistry 56:795–800
22. Choi HJ, Choi YH, Yee SB, Im E, Jung JH, Kim ND (2005) Ircinin-1 induces cell cycle arrest and apoptosis in SK-MEL-2 human melanoma cells. Mol Carcinog 44:162–173
23. Holler U, Konig GM, Wright AD (1999) Three new metabolites from marine-derived fungi of the genera coniothyrium and microsphaeropsis. J Nat Prod 62:114–118
24. Arai M, Kawachi T, Setiawan A, Kobayashi M (2010) Hypoxia-selective growth inhibition of cancer cells by furospinosulin-1, a furanosesterterpene isolated from an Indonesian marine sponge. Chem Med Chem 5:1919–1926
25. Zhou GX, Molinski TF (2006) Manoalide derivatives from a sponge, *Luffariella* sp. J Asian Nat Prod Res 8:15–20
26. Sperry S, Valeriote FA, Corbett TH, Crews P (1998) Isolation and cytotoxic evaluation of marine sponge-derived norterpene peroxides. J Nat Prod 61:241–247
27. Dai J, Liu Y, Zhou YD, Nagle DG (2007) Hypoxia-selective antitumor agents: norsesterterpene peroxides from the marine sponge *Diacarnus levii* preferentially suppress the growth of tumor cells under hypoxic conditions. J Nat Prod 70:130–133
28. Semenza GL (2007) Evaluation of HIF-1 inhibitors as anticancer agents. Drug Discov Today 12:853–859
29. Ueoka R, Nakao Y, Fujii S, van Soest RW, Matsunaga S (2008) Aplysinoplides A-C, cytotoxic sesterterpenes from the marine sponge *Aplysinopsis digitata*. J Nat Prod 71:1089–1091
30. Kobayashi J, Zeng CM, Ishibashi M, Sasaki T (1993) Luffariolides F and G, new manoalide derivatives from the Okinawan marine sponge *Luffariella* sp. J Nat Prod 56:436–439
31. Tsuda M, Endo T, Mikami Y, Fromont J, Kobayashi J (2002) Luffariolides H and J, new sesterterpenes from a marine sponge *Luffariella* species. J Nat Prod 65:1507–1508
32. Mizushina Y, Murakami C, Yogi K, Ueda K, Ishidoh T, Takemura M, Perpelescu M, Suzuki M, Oshige M, Yamaguchi T, Saneyoshi M, Yoshida H, Sakaguchi K (2003) Kohamaic acid A, a novel sesterterpenic acid, inhibits activities of DNA polymerases from deuterostomes. Biochim Biophys Acta 1648:55–61
33. Lange SS, Takata K, Wood RD (2011) DNA polymerases and cancer. Nat Rev Cancer 11:96–110
34. Mizushina Y, Manita D, Takeuchi T, Sugawara F, Kumamoto-Yonezawa Y, Matsui Y, Takemura M, Sasaki M, Yoshida H, Takikawa H (2009) The inhibitory action of kohamaic acid A derivatives on mammalian DNA polymerase beta. Molecules 14:102–121
35. Charan RD, McKee TC, Boyd MR (2001) Thorectandrols A and B, new cytotoxic sesterterpenes from the marine sponge *Thorectandra* species. J Nat Prod 64:661–663
36. Charan RD, McKee TC, Boyd MR (2002) Thorectandrols C, D, and E, new sesterterpenes from the marine sponge *Thorectandra* sp. J Nat Prod 65:492–495
37. Schmidt EW, Faulkner DJ (1996) Palauolol, a new anti-inflammatory sesterterpene from the sponge *Fascaplysinopsis* sp. from Palau. Tetrahedron Lett 37:3951–3954
38. Sima P, Vetvicka V (2011) Bioactive substances with anti-neoplastic efficacy from marine invertebrates: Porifera and Coelenterata. World J Clin Oncol 2:355–361
39. Bae J, Jeon JE, Lee YJ, Lee HS, Sim CJ, Oh KB, Shin J (2011) Sesterterpenes from the tropical sponge *Coscinoderma* sp. J Nat Prod 74:1805–1811
40. Ahn JW, Lee MK, Choi SU, Lee CO, Kim BS (1998) Cytotoxic ophiobolins produced by *Bipolaris* sp. J Micro Biotech 8:406–413
41. Bury M, Girault A, Megalizzi V, Spiegl-Kreinecker S, Mathieu V, Berger W, Evidente A, Kornienko A, Gailly P, Vandier C, Kiss R (2013) Ophiobolin A induces paraptosis-like cell death in human glioblastoma cells by decreasing BKCa channel activity. Cell Death Dis 4:e561
42. Bourguet-Kondracki ML, Longeon A, Debitus C, Guyot M (2000) New cytotoxic isomalabaricane-type sesterterpenes from the New Caledonian marine sponge *Rhabdastrella globostellata*. Tetrahedron Lett 41:3087–3091
43. Paloma LG, Randazzo A, Minale L, Debitus C, Roussakis C (1997) New cytotoxic sesterterpenes from the New Caledonian marine sponge *Petrosaspongia nigra* (Bergquist). Tetrahedron 53:10451–10454
44. Hernandez-Guerrero CJ, Zubia E, Ortega MJ, Luis Carballo J (2006) Sesterterpene metabolites from the sponge *Hyatella intestinalis*. Tetrahedron 62:5392–5400
45. Li J, Xu B, Cui J, Deng Z, de Voogd NJ, Proksch P, Lin W (2010) Globostelletins A-I, cytotoxic isomalabaricane derivatives from the marine sponge *Rhabdastrella globostellata*. Bioorg Med Chem 18:4639–4647
46. Li DD, Guo JF, Huang JJ, Wang LL, Deng R, Liu JN, Feng GK, Xiao DJ, Deng SZ, Zhang XS, Zhu XF (2010) Rhabdastrellic acid-A induced autophagy-associated cell death through blocking Akt pathway in human cancer cells. PLoS One 5:e12176
47. Roy MC, Tanaka J, de Voogd N, Higa T (2002) New scalarane class sesterterpenes from an Indonesian sponge, *Phyllospongia* sp. J Nat Prod 65:1838–1842
48. Pettit GR, Tan R, Cichacz ZA (2005) Antineoplastic agents. 542. Isolation and structure of sesterstatin 6 from the Indian Ocean sponge *Hyrtios erecta*. J Nat Prod 68:1253–1255
49. Chang YC, Tseng SW, Liu LL, Chou Y, Ho YS, Lu MC, Su JH (2012) Cytotoxic sesterterpenoids from a sponge *Hippospongia* sp. Mar Drugs 10:987–997
50. Hahn D, Won DH, Mun B, Kim H, Han C, Wang W, Chun T, Park S, Yoon D, Choi H, Kang H (2013) Cytotoxic scalarane sesterterpenes from a Korean marine sponge *Psammocinia* sp. Bioorg Med Chem Lett 23:2336–2339
51. Corey EJ, Luo G, Lin LS (1997) A simple enantioselective synthesis of the biologically active tetracyclic marine sesterterpene scalarenedial. J Am Chem Soc 119:9927–9928
52. Renner MK, Jensen PR, Fenical W (2000) Mangicols: structures and biosynthesis of a new class of sesterterpene polyols from a marine fungus of the genus *Fusarium*. J Org Chem 65:4843–4852
53. Schumacher M, Cerella C, Eifes S, Chateauvieux S, Morceau F, Jaspars M, Dicato M, Diederich M (2010) Heteronemin, a spongean sesterterpene, inhibits TNF alpha-induced NF-kappa B activation through proteasome inhibition and induces apoptotic cell death. Biochem Pharmacol 79:610–622
54. Cassiano C, Esposito R, Tosco A, Zampella A, D'Auria MV, Riccio R, Casapullo A, Monti MC (2014) Heteronemin, a marine

sponge terpenoid, targets TDP-43, a key factor in several neurodegenerative disorders. Chem Commun (Camb) 50:406–408
55. Aoki S, Higuchi K, Isozumi N, Matsui K, Miyamoto Y, Itoh N, Tanaka K, Kobayashi M (2001) Differentiation in chronic myelogenous leukemia cell K562 by spongean sesterterpene. Biochem Biophys Res Commun 282:426–431
56. Renner MK, Jensen PR, Fenical WJ (1998) Neomangicols: structures and absolute stereochemistries of unprecedented halogenated sesterterpenes from a marine fungus of the genus *Fusarium*. J Org Chem 63:8346–8354
57. De Stefano D, Tommonaro G, Malik SA, Iodice C, De Rosa S, Maiuri MC, Carnuccio R (2012) Cacospongionolide and scalaradial, two marine sesterterpenoids as potent apoptosis-inducing factors in human carcinoma cell lines. PLoS One 7:e33031
58. Youssef DT, Yamaki RK, Kelly M, Scheuer PJ (2002) Salmahyrtisol A, a novel cytotoxic sesterterpene from the Red Sea sponge *Hyrtios erecta*. J Nat Prod 65:2–6
59. Jung HJ, Shim JS, Lee J, Song YM, Park KC, Choi SH, Kim ND, Yoon JH, Mungai PT (2010) Terpestacin inhibits tumor angiogenesis by targeting UQCRB of mitochondrial complex III and suppressing hypoxia-induced reactive oxygen species production and cellular oxygen sensing. J Biol Chem 285:11584–11595
60. Jung HJ, Kwon HJ (2013) Exploring the role of mitochondrial UQCRB in angiogenesis using small molecules. Mol BioSyst 9:930–939
61. Liu Y, Hong J, Lee CO, Im KS, Kim ND, Choi JS, Jung JH (2002) Cytotoxic pyrrolo- and furanoterpenoids from the sponge sarcotragus species. J Nat Prod 65:1307–1314
62. Choi K, Hong J, Lee CO, Kim DK, Sim CJ, Im KS, Jung JH (2004) Cytotoxic furanosesterterpenes from a marine sponge *Psammocinia* sp. J Nat Prod 67:1186–1189
63. De Rosa S, de Giulio A, Crispino A, Iodice C, Tommonaro G (1997) Further bioactive sesterterpenes from the Tyrrhenian sponge *Fasciospongia cavernosa*. Nat Prod Lett 10:267–274
64. Liu Y, Mansoor TA, Hong J, Lee CO, Sim CJ, Im KS, Kim ND, Jung JH (2003) New cytotoxic sesterterpenoids and norsesterterpenoids from two sponges of the genus *Sarcotragus*. J Nat Prod 66:1451–1456
65. Liu Y, Bae BH, Alam N, Hong J, Sim CJ, Lee CO, Sim CJ, Kim ND, Jung JH (2001) New cytotoxic sesterterpenes from the sponge *Sarcotragus* species. J Nat Prod 64:1301–1304