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REVIEW ARTICLE

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An overview on natural farnesyltransferase inhibitors for efficient cancer therapy

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ABSTRACT

As one of the world's five terminally ills, tumours can cause important genetic dysfunction. However, some current medicines for tumours usually have strong toxic side effects and are prone to drug resistance. Studies have found that farnesyltransferase inhibitors (FTIs) extracted from natural materials have a good inhibiting ability on tumours with fewer side effects. This article describes several FTIs extracted from natural materials and clarifies the current research progress, which provides a new choice for the treatment of tumours.

EXECUTIVE SUMMARY

Farnesyltransferase (FTase)

- When Ras gene is activated, it becomes an oncogene with oncogenic activity. Ras protein plays a crucial role in cancer cells. FTase is the first step to activate Ras protein.
- FTIs not only have anti-tumour effects, but also makes great contribution to the treatment of plasmodium falciparum, parasitic diseases and progeria.
- There are still some problems with FTIs, but natural products FTIs are worthy of further research as a new class of low-toxic, safe and effective anticancer drugs.

Summarised natural product-derived FTase inhibitors

- This review summarised several FTIs extracted from natural materials and clarifies their anti-tumour activity (IC_{50} value) and structure, providing a reference for further research on tumour therapy.

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KEYWORDS
Tumour; FTIs; Ras protein; natural materials; inhibitors

1. Introduction

Tumour refers to the local mass formed by abnormal proliferation of local tissue under the action of various tumorigenic factors. It is one of the world's five terminally ill diseases including motor neuron disease, AIDS, leukaemia, and rheumatoid arthritis. Cancer cells have unique properties of invasion and metastasis. Tumours disrupt cell junctions and cell signalling, leading to important gene dysfunction[1]. At present, the main methods for treating tumours are still traditional treatments such as surgical treatment, chemotherapy, and radiation therapy, which usually have strong toxic side effects and are prone to drug resistance. With the development of related disciplines such as molecular biology, research on anti-tumour drugs has also shifted to new anti-tumour drugs targeting multiple links in the mechanism of tumour development. These drugs, for example, targeting cell signalling molecules: including protein tyrosine kinase inhibitors, farnesyltransferase inhibitors (FTIs), mitogen-activated protein kinase (MAPK) signalling pathway inhibitors, cell cycle regulators, etc., are localised to target cell-specific bio-macromolecules, thereby inhibiting the growth and metastasis of tumour cells, rather than killing cells directly. Among them, FTIs are one of the hotspots in recent years, which have attracted the attention of many famous research institutions at home and abroad.

2. Brief introduction to Ras protein and FTIs

The Ras protein mainly regulates the differentiation and proliferation of cells, and is called the "molecular switch" in the transmission of cellular signalling networks. Ras protein is a low molecular weight protein that is distributed inside the cell membrane and has the function of binding to guanine nucleotides, which plays an significant role in cell growth, proliferation, development, differentiation, and cancer cell production[2]. However, if Ras protein is always in an activated state, it will have a continuous stimulating effect on the growth and proliferation of cells, which makes the cells in a state of continuous proliferation or even canceration. Therefore, Ras protein has a very close relationship with tumour generation and development.

As a precursor protein of cytoplasm, Ras protein needs some modifications including prenylation, proteolysis, carboxymethylation,

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Table 1. Anticancer active ingredients of natural materials.

Compound no.	Classifications	Source	Components	FTI IC_{50}	References
1	Quinones	*Tectona grandis* L.	Tecomaquinone I	0.065 μM	Cadelis et al.[3]
2			Derivative	1.1 μM	Cadelis et al.[3]
3			Derivative	9.98 μM	Cadelis et al.[3]
4		*Tectona grandis* L.	Tectol	2.09 μM	Cadelis et al.[3]
5			Derivative	4.4 μM	Cadelis et al.[3]
6			Derivative	1.8 μM	Cadelis et al.[3]
7		*Adocia* sp. sponge	Halenaquinone	0.93 μM	Wang et al.[4]
8			Derivative	0.44 μM	Wang et al.[4]
9			Derivative	0.057 μM	Wang et al.[4]
10			Derivative	0.031 μM	Wang et al.[4]
11		Sponges	Xestosaprol C methylacetal	4.34 μM	Cao et al.[5]
12			orhalquinone	0.40 μM	Cao et al.[5]
13			3-Ketoadociaquinone A	4.19 μM	Cao et al.[5]
14			3-Ketoadociaquinone B	9.27 μM	Cao et al.[5]
15		*A. camphorata*	Antroquinonol	2.986 μM	Ho et al.[6]
16		*Streptomyces* sp.	UCF 116A	1.2 μM	Hara et al.[7]
17			UCF 116B	0.6 μM	Hara et al.[7]
18			UCF 116C	100 μM	Hara et al.[7]
19		*Dichrostachys cinerea*	Dichrostachines A	10 μM	Long et al.[8]
20			Dichrostachines B	40 μM	Long et al.[8]
21			Dichrostachines C	5.7 μM	Long et al.[8]
22			Dichrostachines D	86 μM	Long et al.[8]
23			Dichrostachines E	40 μM	Long et al.[8]
24			Dichrostachines G	17 μM	Long et al.[8]
25			Dichrostachines H	1.8 μM	Long et al.[8]
26			Dichrostachines L	3.2 μM	Long et al.[8]
27			Dichrostachines M	3 μM	Long et al.[8]
28			Dichrostachines O	25 μM	Long et al.[8]
29			Dichrostachines P	7 μM	Long et al.[8]
30			Dichrostachines R	37 μM	Long et al.[8]

and palmification to exert all biological activities[9]. The prenylation of the Ras protein requires three enzymes in turn: farnesyltransferase (FTase), geranylgeranyl transferase I (GGTaseI), and geranylgeranyl transferase II (GGTaseII). Farnesyltran is the first step in post-translational modification of Ras. Therefore, the search for suitable FTIs is an important research direction to inhibit Ras protein and thus inhibit the occurrence of cancer.

FTIs not only have anti-tumour effects, but also have a great contribution to the treatments of *Plasmodium falciparum* and parasitic diseases. In recent years, the study of FTIs has a certain breakthrough in the treatment of premature aging and antiviral field[16,17]. According to the structural analysis and catalytic mechanism of FTase, FTIs can be divided into four types[18]: (1) CAAX (C is cysteine, A is an aliphatic amino acid, and X is serine or methionine) tetrapeptides and their analogues; (2) farnesyl phosphonate (FPP) mimetic; (3) double substrate mimetic; (4) natural product. Natural products have been reported as a major source of lead compounds, and a variety of natural products that could inhibit the activity of FTase have been reported[19]. This article describes several FTIs extracted from natural materials and clarifies the current research progress (Tables 1–4).

3. Natural products FTIs

3.1. Quinones

Quinones are a class of chemical constituents with a quinoid structure, which are mainly classified into four types: benzoquinone, naphthoquinone, phenanthrenequinone, and anthraquinone. This article summarises the inhibition of FTase by natural products and their derivatives isolated from *Tectona grandis* L., sponges, *A. camphorata*, *Streptomyces* sp., and *Dichrostachys cinerea*, with IC_{50} values ranging from 0.031 μM to 100 μM. It is found that phenanthraquinone compounds extracted from *Adocia* sp. Sponge have a better inhibitory effect on FTase, especially compounds **9** and **10**, for their similarity FPP. There are many types and a large number of anthraquinones, including compounds **1** to **6**, **11** to **14** (Figures 1 and 2).

3.1.1. Tectona grandis L

Tectona grandis L. belongs to the *Lamiaceae* family, which is native to Myanmar, Thailand, India, Indonesia, Laos, etc. Currently, it is widely introduced into Yunnan, Guangdong, Guangxi, Fujian, and Taiwan[31]. It plays an important role in pharmacological effects such as antibacterial, anti-arthritic, anti-oxidant, and wound healing[32,33] (Table 4).

Tecomaquinone I was originally extracted from *Tectona grandis* L. by Romanis[43]. It is not only inhibited human and *T. brucei* FTase ($IC_{50} = 0.065$ and 0.112 μM), but also exhibited moderate activity inhibition against *Plasmodium falciparum* ($IC_{50} = 3.44 \pm 0.20$ μM). Cadelis et al.[3] synthesised and analysed a series of derivatives of tecomaquinone I. They found that derivative **2** showed good inhibitory activity against human and *T. brucei* FTase ($IC_{50} = 1.1$ and 2.7 μM), but the inhibitory activity of derivative **3** with the longer side chain added at the same position was significantly reduced.

Sandermann and Dietrichs[44] found a new natural product from *Tectona grandis* L., tectol (**4**). Tectol showed moderate inhibition against FTase ($IC_{50} = 2.09$ μM)[3]. Cadelis et al.[3] synthesised and analysed the derivatives of tectol. They found, as opposed to tecomaquinone I, the derivative with longer side chain (**6**) has stronger inhibitory activity ($IC_{50} = 1.8$ μM). They believed that tecomaquinone I can be used as a novel scaffold to develop more effective FTIs[3].

3.1.2. Sponge

Sponge belongs to *Porifera* and is distributed in the ocean, lakes and streams. Terpenoids and terpenoids extracted from sponges

Table 2. Anticancer active ingredients of natural materials.

Compound no.	Classifications	Source	Components	FTI IC_{50}	References
31	Terpenoids	*Aplidium conicum*	Thiaplidiaquinones A	0.78 μM	Harper et al.[10]
32			Thiaplidiaquinones B	1.22 μM	Harper et al.[10]
33			Derivative	0.14 μM	Harper et al.[10]
34			Derivative	0.054 μM	Harper et al.[10]
35			Derivative	17.3 μM	Cadelis et al.[11]
36			Derivative	14.7 μM	Cadelis et al.[11]
37			Derivative	22 μM	Cadelis et al.[11]
38			Derivative	3.1 μM	Cadelis et al.[11]
39			Derivative	0.17 μM	Cadelis et al.[11]
40			Derivative	1.5 μM	Cadelis et al.[11]
41			Derivative	0.45 μM	Cadelis et al.[11]
42			Derivative	4.7 μM	Cadelis et al.[11]
43			Derivative	7.3 μM	Cadelis et al.[11]
44			Derivative	7.3 μM	Cadelis et al.[11]
45			Derivative	5.8 μM	Cadelis et al.[11]
46			Derivative	5.8 μM	Cadelis et al.[11]
47			Derivative	1.7 μM	Cadelis et al.[11]
48			Derivative	22.3 μM	Cadelis et al.[11]
49			Derivative	22.3 μM	Cadelis et al.[11]
50			Derivative	1.0 μM	Cadelis et al.[11]
51		*Penicillium* sp. FO-3929	Andrastin A	24.9 μM	Omura et al.[12]
52			Andrastin B	47.1 μM	Omura et al.[12]
53			Andrastin C	13.3 μM	Omura et al.[12]
54		*Stachybotrys kampalensis*	Kampanol A	7 μM	Singh et al.[13]
55			Kampanol B	13 μM	Singh et al.[13]
56			Kampanol C	560 μM	Singh et al.[13]
57			Derivative	460 μM	Singh et al.[13]
58		Plant essential oils	*d*-Limonene	5000 μM	Gelb et al.[14]
59		Plant essential oils	*d*-Carvone	5700 μM	Hardcastle et al.[15]
60		Plant essential oils	Perillyl alcohol	1000 μM	Gelb et al.[14]

Table 3. Anticancer active ingredients of natural materials.

Compound no.	Classifications	Source	Components	FTI IC_{50}	References
61	Lactones	*Xanthium strumarium* L.	8-epi-xanthatin	64 μM	Kim et al.[20]
62			8-epi-xanthatin epoxide	58 μM	Kim et al.[20]
63		Unidentified fungus	CP-225917	6 μM	Moorthy et al.[21]
64			CP-263114	20 μM	Moorthy et al.[21]
65		*Artemisia sylvatica*	Arteminolide	0.36 μM	Lee et al.[22]
66			Artanomaloide	22 μM	Lee et al.[23]
67			8-Acetylarteminolide	1.8 μM	Lee et al.[23]
68			Arteminone	85 μM	Lee et al.[23]
69			Arteminone	82 μM	Lee et al.[23]
70			Dehydromatricarin	300 μM	Lee et al.[23]
71		*Artemisia argyi*	Arteminolide B	0.76 μM	Lee et al.[24]
72			Arteminolide C	0.95 μM	Lee et al.[24]
73			Arteminolide D	1.1 μM	Lee et al.[24]
74			Artanomaloide A	105 μM	Lee et al.[24]
75			Artanomaloide C	150 μM	Lee et al.[24]
76	Polycarboxylic acids	*Chaetomella acutiseta*	Chaetomellic acids A	0.055 μM	Gibbs et al.[25]
77			Chaetomellic acids B	0.185 μM	Gibbs et al.[25]
78			Vinyl acid A	2 μM	Singh et al.[26]
79			Vinyl acid B	100 μM	Singh et al.[26]
80			Trans acid A	100 μM	Singh et al.[26]
81			Trans acid B	100 μM	Singh et al.[26]
82			Chaetomellic acid C	0.5 μM	Singh et al.[26]
83			Vinyl acid C	4 μM	Singh et al.[26]
84			Trans acid C	5 μM	Singh et al.[26]
85			Chaetomellic acid D	0.25 μM	Singh et al.[26]
86			Chaetomellic acid E	0.27 μM	Singh et al.[26]
87		*Amaumarcus niger*	Zaragozic acid A	0.25 μM	Dufresne et al.[27]
88			Zaragozic acid B	1 μM	Dufresne et al.[27]
89			Zaragozic acid C	0.15 μM	Dufresne et al.[27]
90			Zaragozic acid D	0.1 μM	Dufresne et al.[27]
91			Zaragozic acid D_2	0.1 μM	Dufresne et al.[27]
92		*Mollisia* sp.	Zaragozic acid D_3	0.6 μM	Tanimoto et al.[28]
93			Zaragozic acid D_3 8-methylester	3.7 μM	Tanimoto et al.[28]
94		*Actinoplanes* sp.	Actinoplanic acid A	0.23 μM	Singh et al.[29]
95			Actinoplanic acid B	0.05 μM	Singh et al.[30]

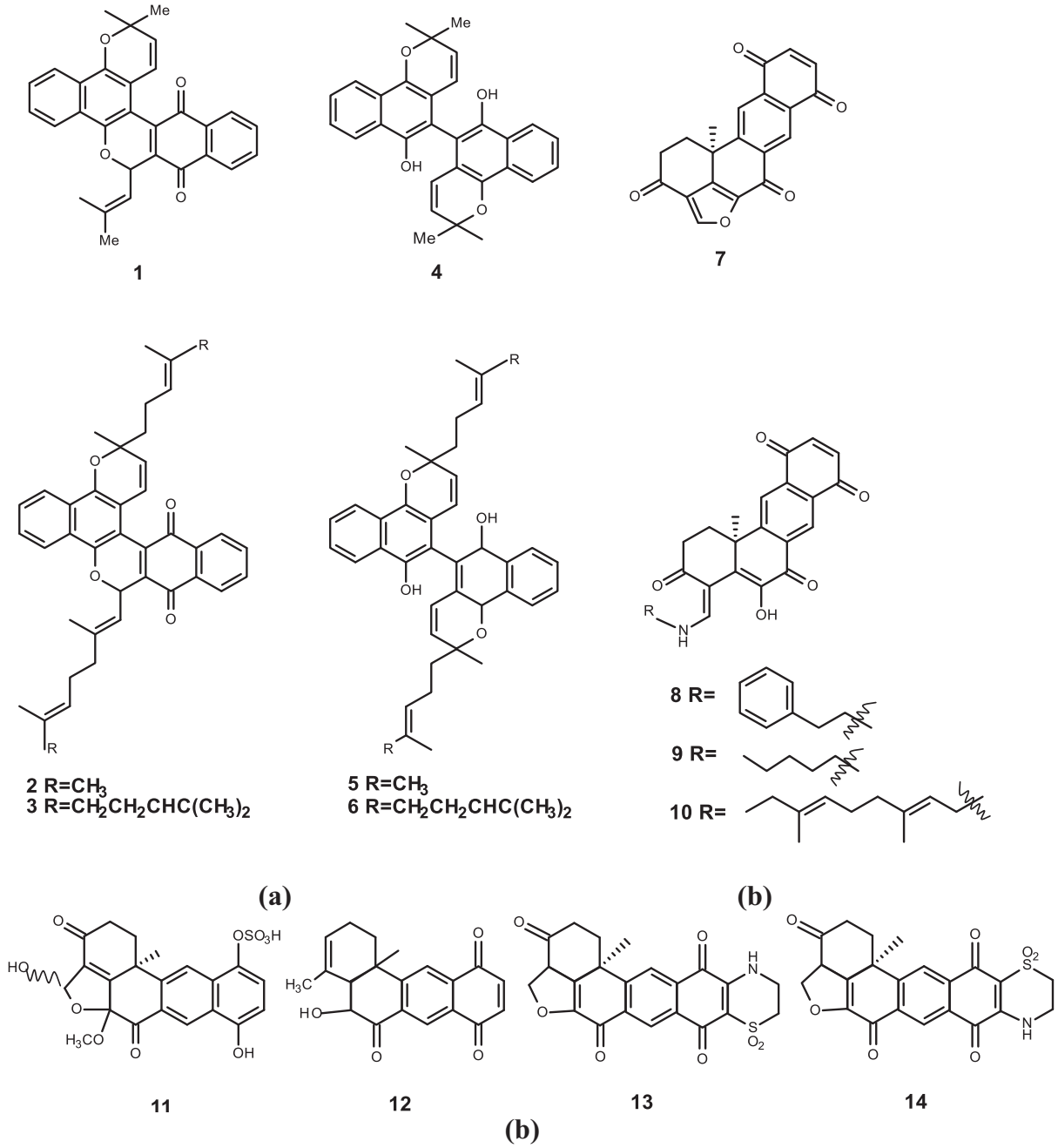


Figure 1. Chemical structures of quinones extracts from (a) *Tectona grandis* L. and their derivatives (**1–6**); (b) sponges and their derivatives (**7–14**).

play an important role in combating malaria, anti-inflammatory, antibacterial, antiviral[45].

Schmitz and Bloor[46] isolated halenaquinone (**7**) from *Adocia* sp. sponge, synthesised the corresponding derivatives on the basis of them, and detected that these inhibitors have certain cytotoxicity. Cao et al.[5] isolated many halenaquinone-type polyketides from marine sponges of the genus *Xestospongia* by bioassay directed fractionation techniques. Wang et al.[4] synthesised some derivatives of halenaquinone, evaluated a series of biological targets including FTase, and determined that halenaquinone and derivative **8**, **9**, and **10** have FTase, phospholipase A2 and *Plasmodium falciparum* inhibition. Among them, compound **10** has the strongest inhibitory effect on FTase ($IC_{50} = 0.031$ μM).

Cao et al.[5,47,48] further isolated the sponges and found two compounds that inhibited FTase, xestosaprol C methylacetal (**11**), and orhalquinone (**12**). Compound **11** possess significant inhibitory activity against human FTase in μM range ($IC_{50} = 4.34$ μM). Compound **12** showed inhibitory activity against human and yeast FTase ($IC_{50} = 0.40$ μM), with a stronger inhibitory effect than xestosaprol C methylacetal. At the same time, Orhalquinone is a moderate growth inhibitor of *P. falciparum*[48]. Besides, Cao et al.[5] also found that 3-ketoadociaquinone A (**13**) and 3-ketoadociaquinone B (**14**) have inhibitory effects on FTase ($IC_{50} = 4.19$ and 9.27 μM) and GGTase ($IC_{50} = 1.08$ and 3.89 μM).

3.1.3. Antrodia camphorata

Antrodia camphorata belongs to *Taiwanofungus* and grows on the inner wall of the decaying heartwood of Taiwan's *Cinnamomum*

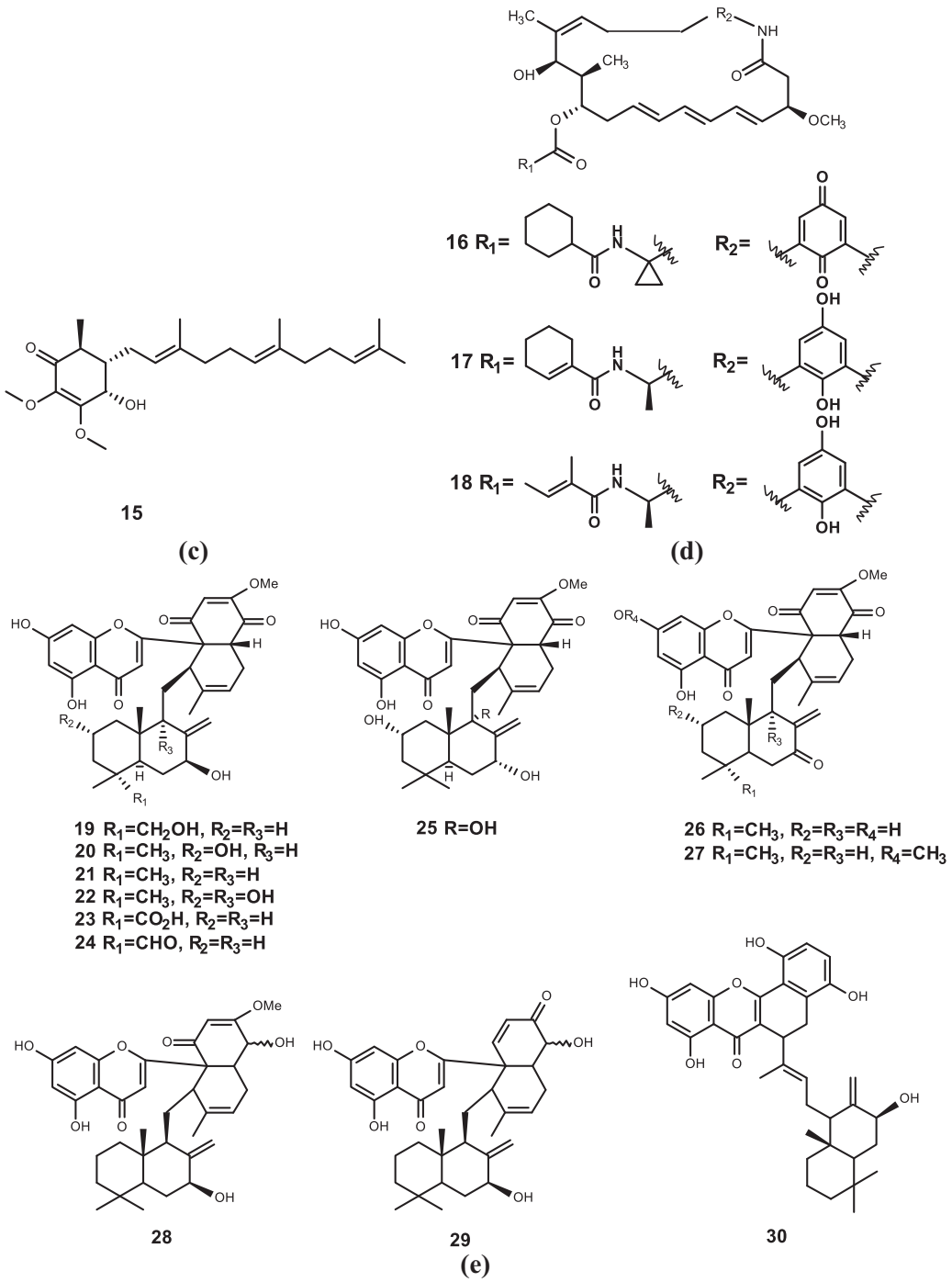


Figure 2. Chemical structures of quinones extracts from (a) *A. camphorata* (**15**); (b) *Streptomyces* sp. (**16–18**); (c) *Dichrostachys cinerea* (**19–30**).

kanehirae, with the effect of lowering cholesterol, anti-cancer, anti-Alzheimer's disease[49–51].

Wu et al.[52] extracted antroquinonol (**15**), a novel compound with anti-inflammatory activities, from the mycelium of *Antrodia camphorata*[53,54]. Ho et al.[6] measured the inhibitory effect of Antroquinonol on various of tumours such as human lung cancer, liver cancer, and leukaemia. Antroquinonol plays a major role in interrupting the function of Ras and Ras-related GTP-binding proteins by inhibiting the activity of FTase and GGTase in cancer cells, ultimately resulting in cell death. At present, antroquinonol is in the phase 2 clinical trials in patients with non-small cell lung cancer[6,55,56].

3.1.4. Streptomyces *sp*

Streptomyces sp. belongs to *Actinomyces* and is widely found in soil. It exhibits a wide range of anti-microbial, anti-parasitic, and anti-oxidant activities and it is an important species for the study of antibiotics[57,58].

Hara et al.[7] isolated UCF 116 compounds from *Streptomyces* sp. Among these compounds, UCF 116A (**16**) and UCF 116B (**17**) have a strong inhibitory effect against bovine brain FTase ($IC_{50} = 1.2$ and 0.6 μM), whereas UCF 116C (**18**) has a weaker inhibitory effect (100 μM)[59]. Compounds **16** and **17** selectively inhibit rabbit reticulocyte lysate FTase ($IC_{50} = 4$ μM) and have a weak inhibitory effect on GTase[60,61]. The kinetic analysis indicated that UCF 116B is

Table 4. Anticancer active ingredients of natural materials.

Compound no.	Classifications	Source	Components	FTI IC50	References
96	Phenolics	*Streptomyces* sp.	Pepticinnamin E	42 μM	Hinterding et al.[34]
97			Derivative	67 μM	Thutewohl et al.[35]
98		*Fusidium griseum*	fusidienol	2.7 μM	Singh et al.[36]
99		*Phoma* sp.	fusidienol A	1.8 μM	Singh et al.[37]
100		*Phoma* sp.	Barceloneic acid A	40 μM	Jayasuriya[38]
101		*Preussia isomera* and *Harmonema dematioides*	Preussomerin G	1.2 μM	Singh et al.[39]
102			Preussomerin H	12 μM	Singh et al.[39]
103			Preussomerin I	17 μM	Singh et al.[39]
104			Preussomerin D	1.2 μM	Singh et al.[39]
105			Deoxypreussomerin A	10 μM	Singh et al.[39]
106			Deoxypreussomerin B	12 μM	Singh et al.[39]
107		*Aspergillus*, *Trichoderma*, and *Penicillium*	Gliotoxin	1.1 μM	Van der Pyl et al.[40]
108		*Cylidrocarpon lucidum*	Cylindrol A	2.2 μM	Singh et al.[41]
109		*Paecilomyces* sp. FO-3684	Kurasoin A	59 μM	Uchida et al.[42]

competitive inhibitor of Ras protein, and UCF 116 compounds are all Ras-competitive and non-CAAX mimetic type inhibitors of FTase. It is further concluded that the substituent at the terminal amide linkage of the three compounds, the cyclohexenecarboxylalanine moiety of the compound **17** and the modification of the substituents at the C-11 site all have a non-negligible inhibitory activity against the FTase. More effective FTIs can be found based on these findings.

3.1.5. *Dichrostachys cinerea*

Dichrostachys cinerea belongs to *Leguminosae* and is native to Africa and India. The trunk can be used for myogenic, analgesic, hemostasis, dysentery, diarrhoea, etc. The bark can be used to treat intestinal parasites, syphilis, and leprosy[62,63].

Long et al.[8] extracted a novel compound from *Dichrostachys cinerea*, which was named dichrostachine A (**19**). To fully study compound **19**, they extracted other secondary metabolites from the roots, stems, and barks of *Dichrostachys cinerea*, a total of 18 compounds (dichrostachine A-R), all of which belong to the meroterpene derivatives. After determining their structures and synthesising the corresponding derivatives, using sch-66336 as the reference compound, they determined that dichrostachine A(**19**), B(**20**), C(**21**), D(**22**), E(**23**), G(**24**), H(**25**), L(**26**), M(**27**), O(**28**), P(**29**), and R(**30**) have the activity of inhibiting Ftase[64]. Compound **25** has the highest inhibitory activity ($IC_{50} = 1.8\ \mu M$). The second is compound **27** ($IC_{50} = 3\ \mu M$), while compound **27** has high cytotoxicity.

3.2. Terpenoids

Terpenes take isoprene unit as the basic structural unit, and are mainly classified into monoterpenes, sesquiterpenes, and diterpenes. This article summarises the inhibition of FTase by natural products and their derivatives isolated from *Aplidium conicum*, *Penicillium* sp., *Stachybotrys kampalensis,* and plant essential oils. Most of the natural products and their derivatives extracted from *Aplidium conicum* have strong FTase inhibitory activity, and the activity varies with the side chain, whereas some monoterpenoids extracted from plant essential oils are weak. Derivatives with side chains of farnesyl group generally have good inhibitory activity. Triterpenoids **51**–**57** are all derived from mildew, and their activities vary greatly with the groups. Some of the monoterpenoids extracted from plant essential oils contain the least amount of isoprene unit and possess the weakest activity. Although terpenes take isoprene unit as the basic structural unit, they are mostly closed-loop structures, and only groups with chain isoprene groups or similar structures can help to inhibit FTase (Figures 3 and 4).

3.2.1. *Aplidium conicum*

Aplidium conicum belongs to *Ascidiacea*, which is widely distributed in the ocean and has good medical value and edible value. Its extracts can promote apoptosis[65,66].

Aiello et al.[67] extracted two marine meroterpenoids, thiaplidiaquinones A (**31**) and thiaplidiaquinones B (**32**), which could induce the apoptosis of Jurkat cells, from the ascidian *Aplidium conicum*. Compound **31** ($IC_{50} = 0.78$ and $0.74\ \mu M$) and Compound **32** ($IC_{50} = 1.22$ and $3.04\ \mu M$) have inhibitory effects against both human and *T. brucei* FTase. Harper et al.[10] obtained the corresponding dioxothiazine isomers (**33**) and (**34**). Compounds **31**, **33**, and **34** were identified to be potent inhibitors of human and *T. brucei* FTase, and the IC50 values are in the range of nM. Compounds **33** and **34** have moderate inhibitory activity against *Plasmodium falciparum*, and compound **33** also has moderate antiproliferative activity against melanocyte cell lines. To further investigate the structure–activity relationship of thiaplidiaquinones (**31**–**34**), Cadelis et al. synthesised a series of derivatives (**35**–**50**), among which 17 derivatives have inhibitory activity against FTase. The test results show that the derivatives with the farnesyl side chain (**39**–**42**) have stronger FTase inhibitory activity than the derivatives with the isoprene side chain (**35**–**38**)[11].

Grayfer et al.[68] found that the modification of the prenylated side chain of the natural product can regulate biological activity. For example, an increase in the number of prenyl units on the side chain of mallotojaponin B may enhance anti-malarial and FTase inhibitory activity. Whereas studies on tecomaquinone I indicated that this increase leads to a decrease in FTase activity. After synthesis and determination of derivatives of compounds **31** and **32**, it was found that this series of compounds have strong or weak inhibitory effects on FTase, and most of the compounds also have moderate antimalarial activity.

3.2.2. Penicillium *sp*

Penicillium sp. belongs to *Trichocomaceae* and grows on decaying fruits, vegetables, meat, and various moist organic substances. Its metabolites show excellent antibacterial and anti-inflammatory activities, moreover, good killing effect on larvae such as *Culex quinquefasciatus*[69,70].

Shiomi et al.[71] extracted andrastin A (**51**), andrastin B (**52**), and andrastin C (**53**) from *Penicillium* sp. FO-3929. These three compounds have inhibitory effects on FTase in a dose-dependent manner ($IC_{50} = 24.9$, 47.1, and $13.3\ \mu M$)[12].

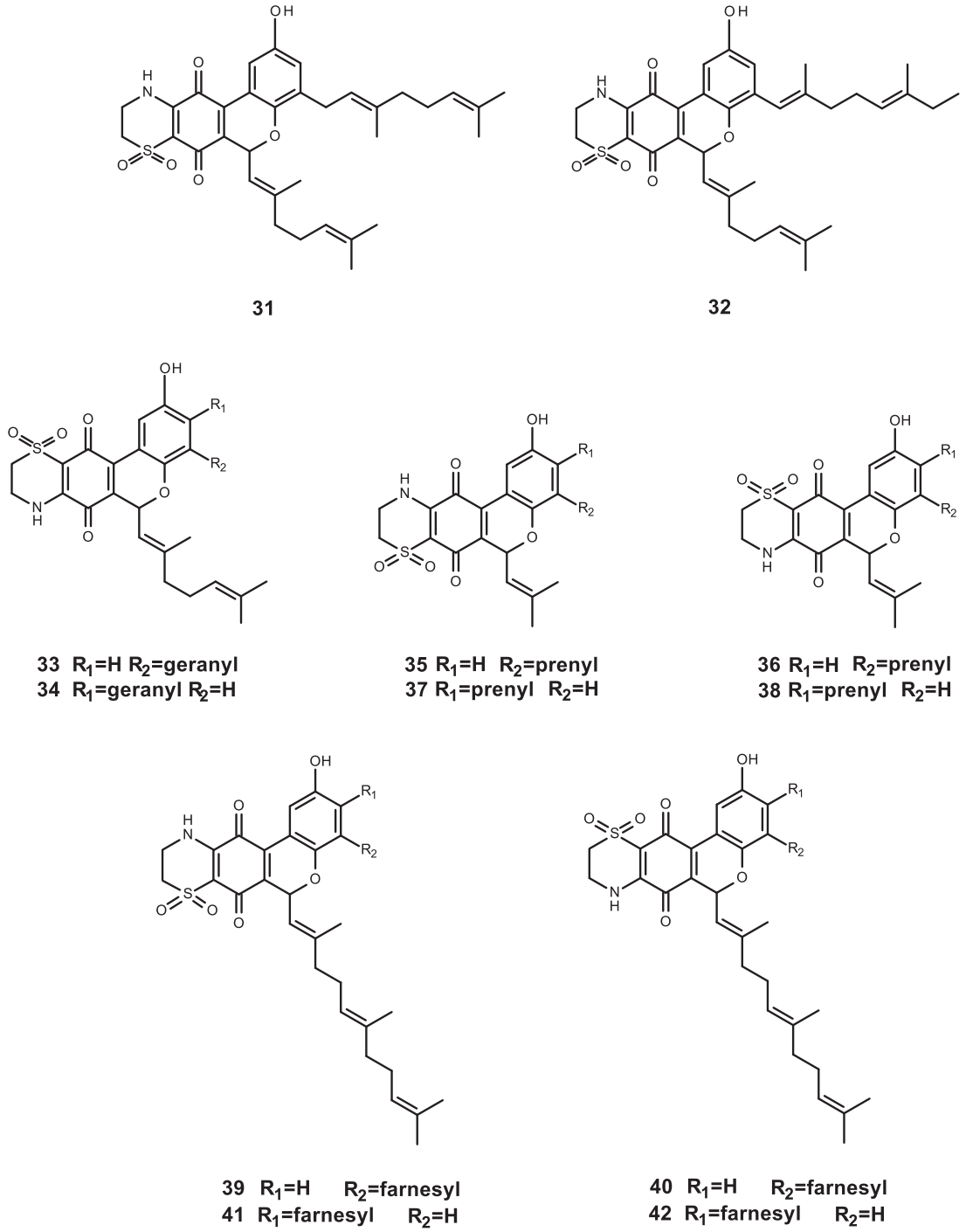


Figure 3. Chemical structures of terpenoids extracts from *Aplidium conicum* and their derivatives (**31–42**).

3.2.3. Stachybotrys kampalensis

Stachybotrys kampalensis belongs to *chartrum*, which is commonly found in soil and can use plants to produce cellulose[72]. *Stachybotrys* can help the treatment of cancer[73].

Singh et al.[13] isolated kampanol A-C (**54**–**56**) from *Stachybotrys kampalensis* and synthesised a derivative of **56**. Compounds **54**, **55** are found to have inhibitory activity against human recombinant FPTase by biological activity assay ($IC_{50} = 7$ and 13 μM). Nevertheless, **56** and its derivative (**57**) have weak inhibitory activities ($IC_{50} = 560$ and 460 μM). Besides, none of the four compounds have inhibitory activity against GGTase.

3.2.4. Plant essential oils

Plant essential oils are extracted from a variety of plants. Major of them are monoterpenoids. These compounds have antibacterial and insecticidal effects[74]. Several monoterpenoids described here have a certain inhibitory effect on FTase.

Crowell et al.[75] extracted the monoterpenoid *d*-limonene (**58**), one of the end products of the metabolism of mevalonate in plant cells, which is widely found in orange peel and some plant essential oils. Compound **58** is one of the few natural anti-tumour products known to have both chemopreventive and chemotherapeutic effects. Besides, *d*-limonene is also a very effective

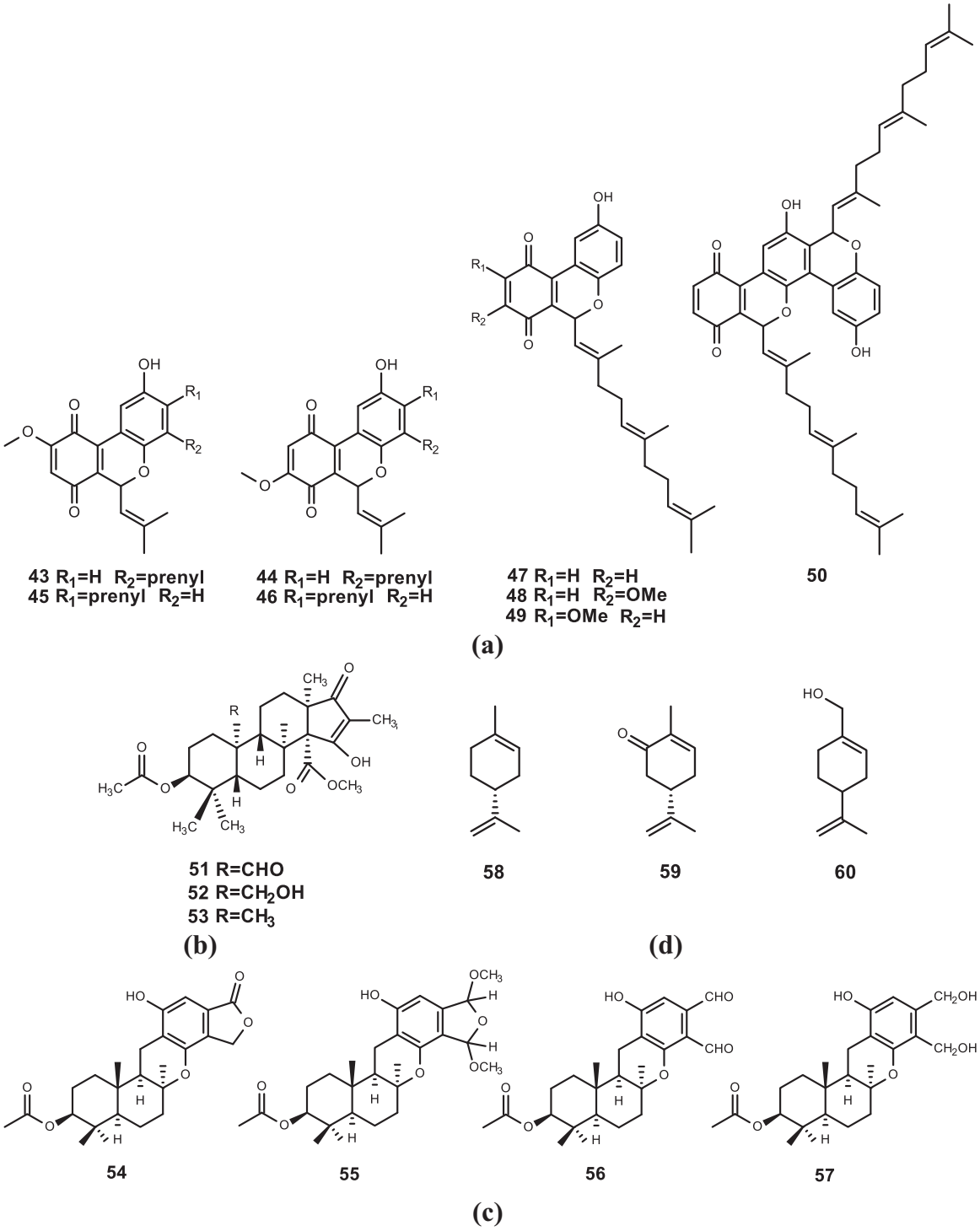


Figure 4. Chemical structures of terpenoids extracts from (a) *Aplidium conicum* and their derivatives (**43–50**); (b) *Penicillium* sp. (**51–53**); (c) *Stachybotrys kampalensis* and their derivatives (**54–57**); (d) plant essential oils (**58–60**).

chemotherapeutic agent, which can cause 80% complete regression of rat breast cancer induced by chemical factors[76–78]. Currently, *d*-limonene has entered phase I clinical studies in the UK[79].

Crowell et al.[80] demonstrated that *d*-carvone (**59**), which is a *d*-limonene analogue, can inhibit cell growth. Hardcastle et al.[15] suggested that compound **59** may be a metabolite of limonene *in vivo*, a potential FTI ($IC_{50} = 5700$ μM).

Perillyl alcohol (**60**), similar to *d*-limonene, is a monoterpenoid derived from the essential oils of cherries and other plants. It also has the effect of inhibiting cell growth and weak FTase and GGTase inhibition ($IC_{50} = 1000$ and 700 μM)[14,81].

3.3. Lactones

Lactone refers to the organic matter produced by dehydration of both carboxyl group and hydroxyl group in the same molecule, which is mainly classified according to the size of the ring. We summarise the inhibition of FTase by natural products

and their derivatives isolated from *Xanthium strumarium* L., unidentified fungus, and *Artemisia*. In such compounds, the IC_{50} value of the natural product as a function of side chain groups varies widely. When the groups are the same, the activity of the compounds which are isomers will also vary greatly. For example, the compounds **71**, **72** and the compounds **74**, **75** are positional isomers, but their activities differ by more than 100-fold (Figure 5).

3.3.1. Xanthium strumarium L

Xanthium strumarium L. belongs to *Compositae* and is widely distributed in China. It can be used as raw material for paint, soap, and linoleum. Its fruit extracts have the ability of anti-bacterial, anti-oxidation, anti-diabetes, and preventing arthritis[82,83].

Kim et al.[20] extracted two xanthanolide sesquiterpene lactones, 8-epi-xanthatin (**61**) and 8-epi-xanthatin epoxide (**62**) from the leaves of *Xanthium strumarium* L. The concentration of compound

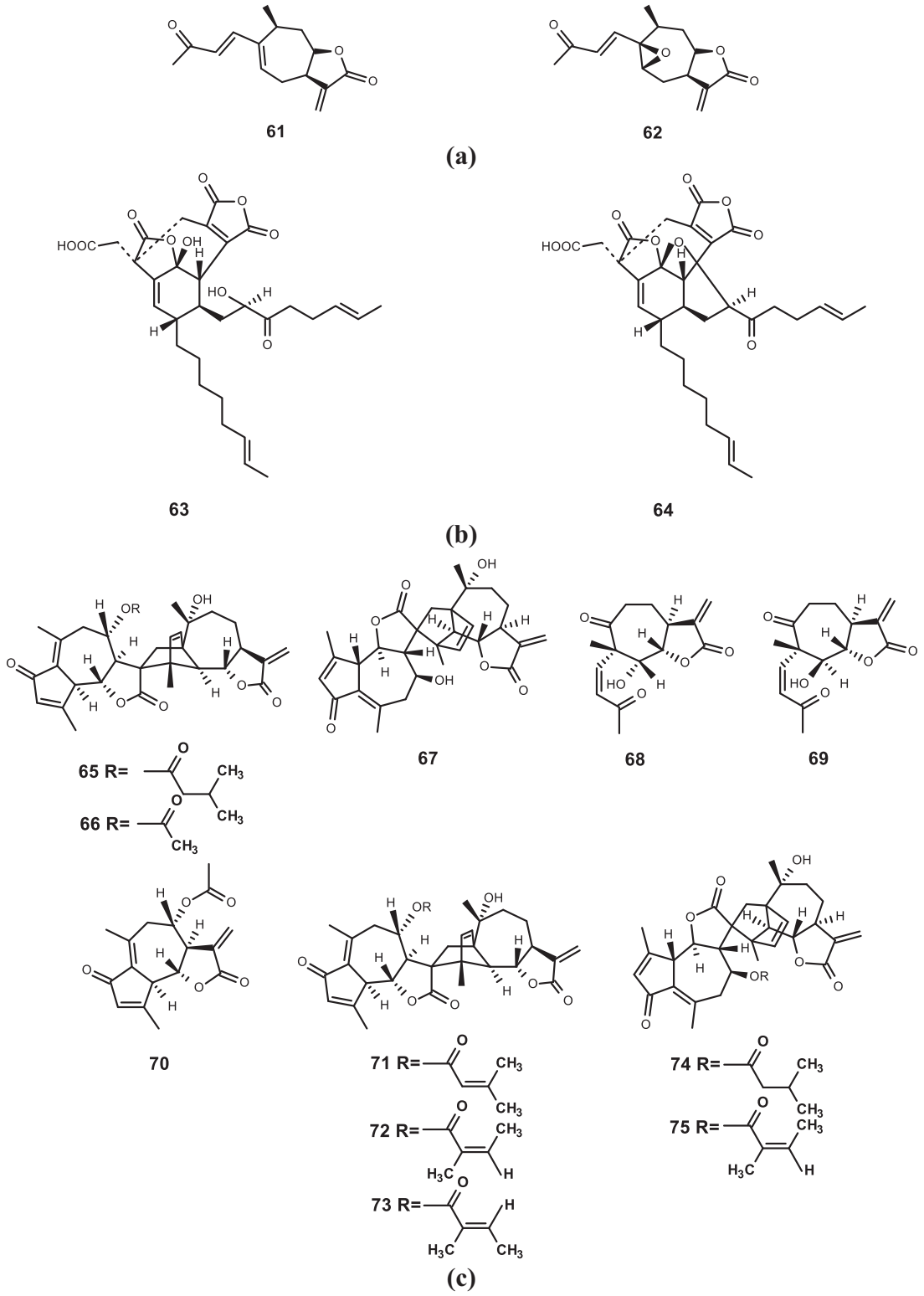


Figure 5. Chemical structures of lactones extracts from (a) *Xanthium strumarium* L. (**61–62**); (b) unidentified fungus (**63–64**); (c) *Artemisia* (**65–75**).

61 required to obtain FTase inhibition is higher than that of compound **62** ($IC_{50} = 64$ and 58 μM). The results of in-depth study of compound **61** show that compound **61** can inhibit the growth of *T. brucei rhodesiense*, *T. cruzi*, *L. donovani*, and *P. falciparum* with IC_{50} values of 0.33, 11.3, 0.6, and 6.5 μM, respectively. However, the cytotoxicity of compound **61** reached 22.1 μM for rat myoblast cells. In other words, its side effects are great[84].

Matsuo et al.[85] separated two milder compounds from *Xanthium strumarium* L. leaves. Although the inhibitory activities of the two compounds were weaker than that of the compound **61**, their side effects were smaller and safer[86,87].

3.3.2. Unidentified fungus

Dabrah et al.[21,88,89] found two compounds CP-225917 (**63**) and CP-263114 (**64**) from unidentified fungi, which have some characteristics of *Phoma* sp. The structures of the two compounds were analysed by means of extensive NMR measurements, UV spectra, and FT-IR spectra[89]. It was verified by experiments that both compounds inhibited FTase in the brain of mice ($IC_{50} = 6$ and 20 μM).

3.3.3. Artemisia

As *Compositae*, *Artemisia* is extremely strong and widely distributed, which is distributed in temperate regions of the northern hemisphere. *Artemisia* has good medicinal value, can be used to treat malaria and cancer. In addition, *Artemisia* also has antibacterial and anti-oxidant effects[90,91].

Lee et al.[22] isolated a compound from the leaves of *Artemisia sylvatica* Maxim in 1998. It was determined to be arteminolide (**65**) by NMR, IR, HREIMS, NOESY spectrum, and mass spectral data. Compound **65** has broad biological activity and selectively inhibits FTase ($IC_{50} = 0.36$ μM)[92–94].

Later, Lee et al.[23] isolated five compounds from the methanol extract of *Artemisia sylvatica* in 2000. After testing and comparing the spectral data with the reported spectral data[95], it was confirmed that the five compounds were artanomaloide (**66**), 8-acetylarteminolide (**67**), arteminone (**68** and **69**), and dehydromatricarin (**70**). All the five belong to sesquiterpene lactone. Among them, compounds **68** and **69** are identified as stereoisomers. The inhibitory effects of five compounds on FTase were examined by scintillation proximity assay (SPA). The results show that compound **67** selectively inhibited recombinant rat FTase ($IC_{50} = 1.8$ μM) and weaker inhibitory activity against recombinant rat GGTase ($IC_{50} \gg 100$ μM). Compounds **66**, **67**, **68**, and **69** also had some inhibitory effects on FTase ($IC_{50} = 22$, 85, 82, and 300 μM). This result is important for studying the pharmacological activities of sesquiterpene lactones. Due to the special structure of 8-acetylarteminolide, Lee et al. speculated that it might be a useful lead compound for the development of anticancer drugs. Subsequent studies show that 8-acetylarteminolide does have an inhibitory effect against tumour cells[96,97].

Lee et al.[24] isolated some compounds from *Artemisia argyi* and obtained the corresponding chemical structure through experiments in 1998. They renamed the arteminolide (**65**) as arteminolide A, and the other compounds were named arteminolide B (**71**), arteminolide C (**72**), arteminolide D (**73**), artanomaloide A (**74**), and artanomaloide C (**75**). Among them, compounds **74**, **75** are regioisomers. *In vitro* enzyme assays and kinetic experiments revealed that compounds **71**–**73** have strong inhibitory effect on recombinant human FTase with IC_{50} values ranging from 1.7 to 1.1 μM. However, the IC_{50} values of artanomaloides are all over 100 μM. Arteminolides and artanomaloides have almost no inhibitory activity against rat squalene synthase and recombinant rat GGTase.

3.4. Polycarboxylic acids

Polycarboxylic acids are a class of carboxylic acids containing a plurality of carboxyl groups. We summarises the inhibition of FTase by polycarboxylic acids isolated from *Chaetomella* sp., *Amaumarcus niger*, *Mollisia* sp., and *Phoma* sp. The inhibitions of these natural products are significant. After analysing the activity and structure of each compound, it was found that several polycarboxylic acid compounds in this review had groups similar to FPP and could compete with FPP to inhibit FTase, so almost all these polycarboxylic acids compounds had good inhibitory activity. The side chain groups of polycarboxylic acids have a great influence on the activity. For example, the cis-orientation of dicarboxylic acid and the CH on the alkyl side can make the inhibitory effect more significant, while the cis-diacid composed of shorter alkyl chain can make the compound lose its inhibitory activity (Figures 6 and 7).

3.4.1. Chaetomella *sp*

Chaetomella sp. belongs to *Sphaeropsidaceae,* which uses many plants as its host to survive and has good adaptability to various environment, thus it is distributed all over the world[98]. *Chaetomella* sp. is an important material for the production of Taxol[99], which has a certain contribution to the treatment of cancer.

Singh et al.[100] extracted chaetomellic acids A (**76**) and B (**77**) from *Chaetomella acutiseta* and confirm that they can inhibit recombinant human FTase. Subsequently, compounds **76** and **77** were confirmed to have reversible inhibitory abilities against FTase ($IC_{50} = 55$ and 185 nM), and selective inhibitory abilities against bovine brain GGTase ($IC_{50} = 92$ and 54 μM)[25]. Lingham et al.[101] further verified that compounds **76** and **77**, similar to FPP, are reversible inhibitors of FTase. Singh et al.[26] synthesised the isomeric diacids (**78**, **79**, **80**, **81**) of chaetomellic acids A and B, together with C-12 chain compound chaetomellic acid C (**82**) and its isomers (**83**, **84**). They also found chaetomellic acids D (**85**) and E (**86**) from a mycelial broth. These compounds all have strong or weak FTase inhibitory abilities, but no inhibitory activity against GGTase. The results of their work show that the cisoid orientation of the dicarboxylic acid and the alkyl chain of the appropriate length play an important role in the inhibitory activity against FTase. The *trans*- and *vinyl*-diacids reduce the inhibitory activity of the compound, and the *cis*-diacids consisting of a shorter alkyl chain were inactive against FTase.

3.4.2. Amaumarcus niger, Mollisia *sp., and* Phoma *sp*

Amaumarcus niger is a keratinophilic fungus which is mostly distributed in the soil. Most of the extracts from *Amaumarcus niger* have strong activity. *Mollisia* sp. belongs to the *Mollisiaceae* and is mainly distributed in warm and humid areas. Although *Mollisia* sp. causes some diseases, some of its extracts can be used as new antibiotics and have contributed to the field of medicine[102]. *Phoma* sp. is an endophytic fungus widely distributed in the ocean. It has considerable application value. Its isolated products can achieve the effect of treating cancer by inducing apoptosis and autophagy of cancer cells[103]. For example, terpenoids extracted from its culture medium show good antiviral activity[104], and its metabolites can be used to prepare herbicides[105].

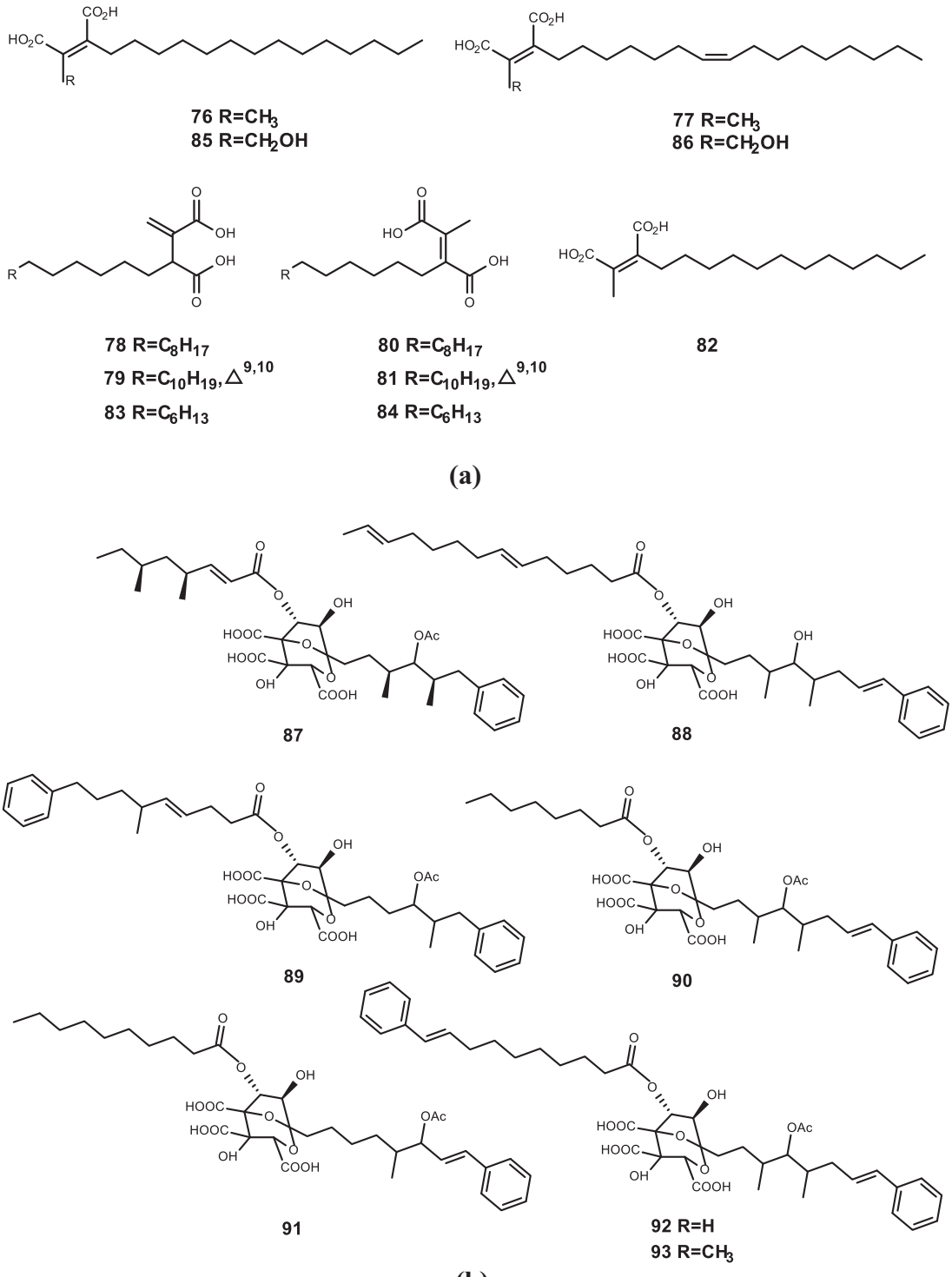
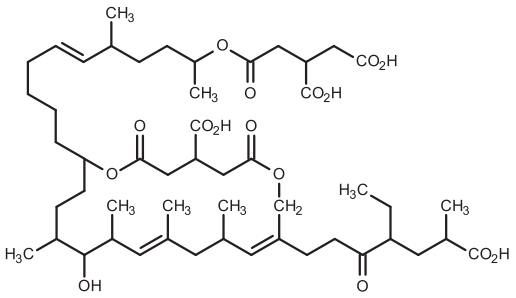


Figure 6. Chemical structures of polycarboxylic acids extracts from (a) *Chaetomella acutiseta* and their derivatives (**76–82**); (b) *Amaumarcus niger* and *Mollisia* sp. (**87–93**).

Zaragozic acid A (**87**), B (**88**), C (**89**), D (**90**), and D_2 (**91**) extracted from keratinophilic fungus *Amaumarcus niger* belong to tricarboxylic acid. The structure was identified by 2D NMR and mass spectral experiments[106–109]. The five compounds all have FTase inhibitory activity, by competing with FPP. Among them, compounds **89**, **90**, and **91** have the strongest activity ($IC_{50} = 150$, 100, and 100 nM), whereas compound **87** and **88** have relatively weak activity ($IC_{50} = 250$ and 1000 nM)[25,27]. Tanimoto et al.[110] extracted zaragozic acid D_3 (**92**) and zaragozic acid D_3 8-methyl-ester (**93**) from the fungus *Mollisia* sp. Both of the compounds have strong inhibitory activities on FTase and GGTase[28]. Pedretti et al.[111] performed a detailed docking analysis of zaragozic acid extracted from *Phoma* sp. by molecular docking and found that zaragozic acid have strong FTase inhibitory ability by interacting with residues at two FPP binding sites.

3.4.3. Actinoplanes *sp*

Actinoplanes sp. belongs to *Micromonosporaceae*, which grows in soil, fresh water, and plant remnants. Its hyphae produce a variety of antibiotics against bacteria and tumours[112,113].



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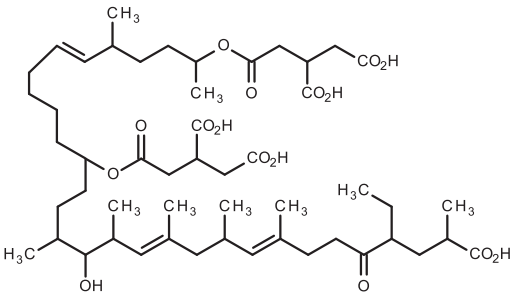

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Figure 7. Chemical structures of polycarboxylic acids extracts from *Actinoplanes* sp. and their derivatives (**94–95**).

Singh et al.[29] originally extracted actinoplanic acid A (**94**) from *Actinoplanes* sp. and determined its structure. Compound **94** was found to compete with FPP and was also a selective inhibitor of FTase ($IC_{50} = 230$ nM). Subsequently, actinoplanic acid B (**95**) was extracted from *Actinoplanes* sp., which also exerts selective and competitive inhibition of FTase and has stronger inhibitory activity ($IC_{50} = 50$ nM)[30,114]. When analysing the structure, we found that compounds **94** and **95** carried more groups similar to FPP, just as Singh et al. found that they could compete with FPP to inhibit FTase, with strong inhibitory activity.

3.5. Phenolics

The phenolic compound refers to a compound having a hydroxyl group on an aromatic hydrocarbon and is classified into monohydric phenol and polyhydric phenol. This review summarises phenolic compounds isolated from several fungi with a small IC_{50} difference and similar inhibitory abilities against FTase. After observing of the structure and activity of the compounds, it was found that compounds **96** and **97** had more complicated structures than other phenolic compounds and were less effective in inhibiting FTase (Figures 8 and 9).

3.5.1. Streptomyces *sp*

Streptomyces sp. is the highest *Actinomyces* and has a good adaptability to the environment. It is of great value to the development of antibiotics and cancer treatment.

Hinterding et al.[115] isolated pepticinnamin E (**96**) from secondary metabolites of *Streptomyces* sp. It is the first Ras protein substrate competition inhibitor derived from natural products. What is more, subsequent studies show that it is a dual substrate (Ras protein and FPP) competition inhibitor ($IC_{50} = 42$ μM)[34,115,116]. Structurally, compound **96** mimics the two substrates of FTase, CAAX, and FPP.

Thutewohl and Waldmann[35] synthesised a library of compounds including 51 analogues based on the structure of compound **96** by a change in eight structural parameters. Among them, the seventh derivative (**97**) has an inhibitory activity similar to that of compound **96** ($IC_{50} = 67$ μM).

3.5.2. Fusidium *sp*

Fusidium sp. belongs to *Moniliaceae* and has important medical value. The antibiotic fusidic acid extracted from *Fusidium* sp. has been used for disease treatment since 1962[117,118]. Fusidic acid not only has good *in vitro* antibacterial effect, but also has strong anti-inflammatory effects *in vivo*[119].

Singh et al.[36] extracted fusidienol (**98**) from *Fusidium griseum*, which inhibited bovine brain FTase and human FTase ($IC_{50} = 0.3$ and 2.7 μM).

Fusidienol A (**99**) is an FTase inhibitor extracted from *Phoma* sp., which is similar in structure and function to compound **98**. Compound **99** has a strong inhibitory activity on recombinant human FTase ($IC_{50} = 1.8$ μM) but does not inhibit GGTase well[37].

3.5.3. Phuma *sp*

As an endophytic fungus, *Phuma* sp. has the effect of treating cancer and antiviral activity.

Jayasuriya et al.[38] extracted three natural products from *Phuma* sp. The structure and activity of these compounds were determined experimentally. Only barceloneic acid A (**100**) was found to have FTase inhibitory activity ($IC_{50} = 40$ μM).

3.5.4. Preussia *sp. and* Harmonema dematioides

Preussia sp. is a new Chinese strain discovered in 2013 and belongs to endophytic fungi. Its isolates have strong antiplasmodial, antibacterial, and antioxidant activities[120,121]. *Harmonema dematioides* is also an endophytic fungus. It produces secondary metabolites that inhibit the biosynthesis of sterols and thus have a good therapeutic effect on heart disease[122].

Zink et al.[39] studied the structure–activity relationships of preussomerin G (**101**), H (**102**), I (**103**), D (**104**), deoxypreussomerin A (**105**) and B (**106**) extracted from the coprophilous fungus *Preussia isomera*, and the endophytic fungus *Harmonema dematioides*[123–125] which are fungal metabolites. They have a certain inhibitory activity on FTase. Among them, compound **101** has the strongest activity, not only against FTase, but also GGTase ($IC_{50} = 1.2$ and 20 μM).

3.5.5. Aspergillus, Trichoderma, *and* Penicillium

Aspergillus belongs to *Aspergillaceae* and is widely distributed in nature. Although it causes food spoilage and is extremely toxic, it has a key role in food fermentation. *Aspergillus* also has a positive contribution to antibacterial effects[126]. *Trichoderma* belongs to *Hypocreaceae* and is mainly distributed in rot, seeds, plant residues, organic fertilisers, soil, and air. *Trichoderma* has good medicinal value. For example, it can be used to produce cellulase[127], producing antibiotics, and so on[128]. Living on saprophytic life, *Penicillium* sp. can cause food to rot, but it also has certain antibacterial and anti-inflammatory effects.

Shah et al.[40,129] extracted gliotoxin (**107**) from *Aspergillus*, *Trichoderma*, and *Penicillium*, which is a sulphur-containing

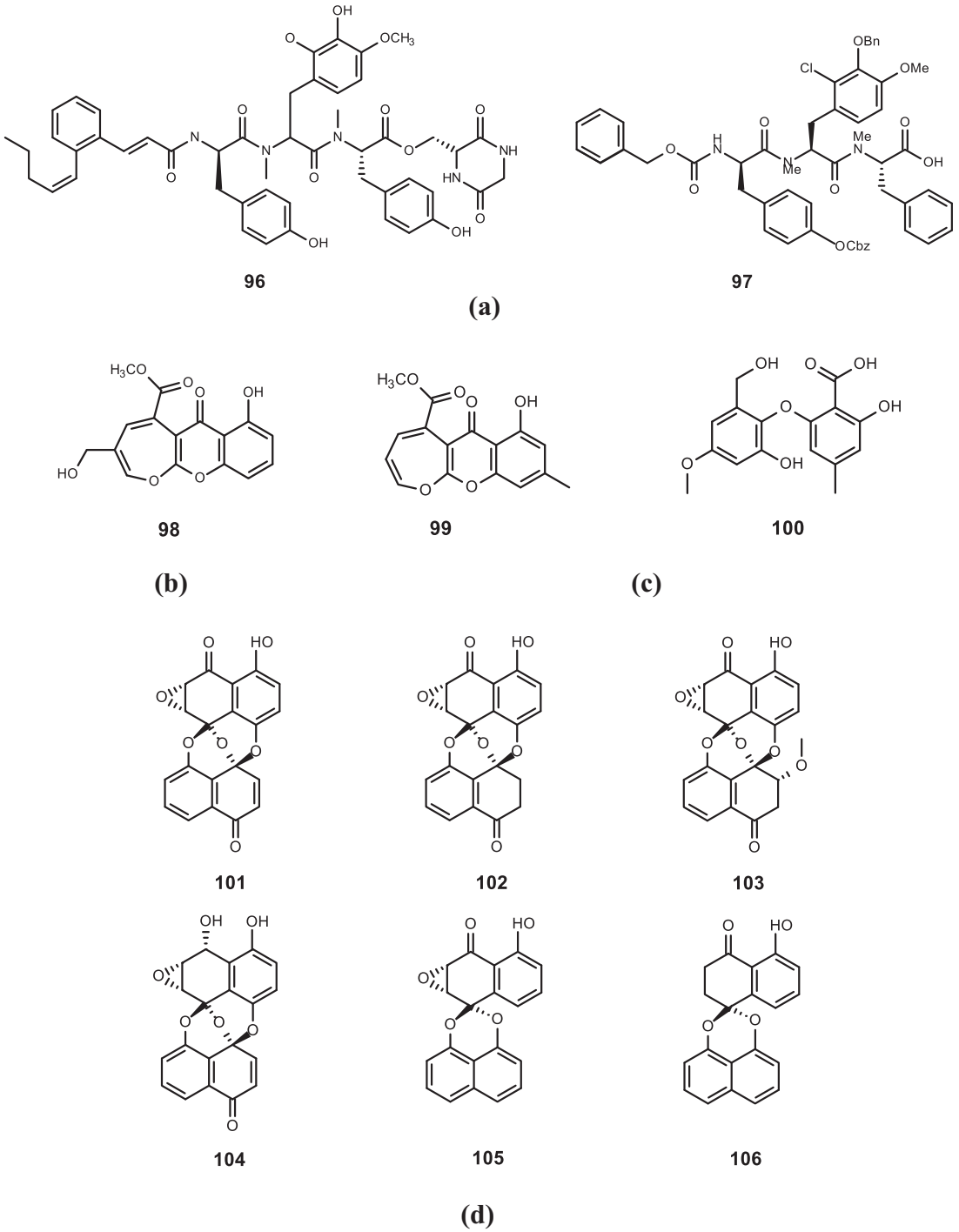

Figure 8. Chemical structures of phenolics extracts from (a) *Streptomyces* sp. (**96–97**); (b) *Fusidium griseum* (**98**); (c) *Phoma* sp. (**99–100**); (d) *Preussia isomera* and *Harmonema dematioides* (**101–106**).

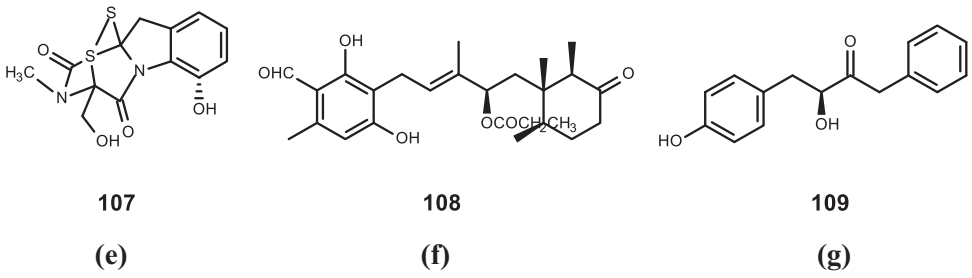

Figure 9. Chemical structures of phenolics extracts from (e) *Aspergillus*, *Trichoderma*, and *Penicillium* (**107**); (f) *Cylidrocarpon lucidum* (**108**); (**g**) *Paecilomyces* sp. (**109**).

mycotoxin. Compound **107** has modest FTase inhibitory activity ($IC_{50} = 1.1\ \mu M$).

3.5.6. *Cylidrocarpon lucidum*

Cylidrocarpon lucidum is a fungus with excellent medicinal value. Its metabolites can form cyclosporin for treating rheumatoid arthritis[130].

Singh et al.[41] extracted cylindrol A (**108**) from *Cylidrocarpon lucidum*, which is a bicyclic resorcinaldehyde cyclohexanone propionate derivative. It could inhibit bovine FTase ($IC_{50} = 2.2\ \mu M$).

3.5.7. Paecilomyces *sp*

Paecilomyces sp. belongs to *Discellaceae*, and its research is still not very thorough. It is a group of fungi that are only found in asexual or sexual stages. Its extracts have a considerable effect on antileishmanial and enhanced immunity[131,132].

Uchida et al.[42] extracted kurasoin A (**109**) from a cultured broth of *Paecilomyces* sp. FO-3684, and determined the structure of this compound for the first time. It was found to have a dose-dependent inhibition against FTase ($IC_{50} = 59\ \mu M$).

4. Future perspective

So far, many compounds with FTase inhibitory activity have been discovered and synthesised. What is more, many of them are now in the clinical trials. Oral FTIs developed in recent years have high bioavailability and selective antitumor activity *in vivo*, and their potential effects may eventually be used to treat malignant tumours in humans. FTIs have also made significant achievements in the treatment of diseases such as premature aging and leukaemia[133–135].

It is worth noting that half of the compounds listed here with IC_{50} values less than $1\ \mu M$ are from belong to polycarboxylic acid compounds. The importance of polycarboxylic acid compounds in the inhibition of FTase activity was demonstrated. The structural similarity of these polycarboxylic acid compounds to FPP may be the main reason for their effective FTase inhibitory activity. In this review, compounds containing chain groups are similar to FPP, which can compete with FPP to inhibit FTase. However, FPP is also substrate of other enzymes, FPP-competitive inhibitors may inhibit the physiological function of them, causing some harm to the human body. As far as the current results concerned, natural products FTIs are worthy of further research as a new class of low toxicity, safe, and effective anticancer drugs. Apart from further structural modifications based on the existing structural types to enhance the selectivity and *in vivo* activity of FTIs, a rich library of natural compounds is also worthy of attention. In recent years, many FTIs of novel structures have been found in natural products. It is expected that FTIs will be a promising field of research for new anticancer drugs, and will provide more new options for the clinical treatment of malignant tumours.

Disclosure statement

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