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REVIEW ARTICLE



# Advance in biological activities of natural guaiane-type sesquiterpenes

Gang-Hua Ma[1] · Kai-Xian Chen[1,2] · Liu-Qiang Zhang[1] · Yi-Ming Li[1]

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## Abstract

Belonging to the terpenes family, sesquiterpenes represent a group of natural compounds with diverse skeletal types. Given their unique structural features and various functional groups, these compounds possess numerous biological activities and have received increasing interest in recent years. Guaiane-type sesquiterpenes are a special category of sesquiterpenes with various biological activities, such as antitumor, anti-inflammatory, and antibacterial. Mipsagargin, a prodrug of thapsigargin, could be used in the treatment of glioblastoma multiforme and hepatocellular carcinoma, and has completed the phase II clinical trials. Guaiane-type sesquiterpenes are not only abundant but also diverse, widely distributed, and complex, and have variable structures. To our knowledge, there is no review of guaiane-type sesquiterpenes in extant literature. This review summarizes the distribution of guaiane-type sesquiterpenes in plants, the possible biogenic pathways and chemical structures as well as the research progress on their biological activities from 1990 to 2018. Guaiane-type sesquiterpenes are present in approximately 70 genera of 30 plant families (e.g., Asteraceae, Lamiaceae, Thymelaeaceae, and Zingiberaceae); they can be classified into 12,6-guaianolides, 12,8-guaianolides, pseudoguaianolides, tricycle guaiane-type sesquiterpenes, dimers or trimers containing guaiane-type sesquiterpenes mother nuclei, variant guaiane-type sesquiterpenes, and other guaiane-type sesquiterpenes. Among them, 12,8-guaianolides exerted the broadest biological activity.

**Keywords** Guaiane-type sesquiterpenes · Asteraceae · Guaianolides · Anti-inflammation · Antitumor

## Introduction

Sesquiterpenes are a class of terpenes that consist of three isoprene units and often have the molecular formula $C_{15}H_{24}$. Like monoterpenes, sesquiterpenes may be acyclic or contains rings, with many unique combinations. Sesquiterpenes are the most distinct group in terms of the structure of the terpenoids, most of which exert biological activities (Hou et al. 2014). Guaiane-type sesquiterpenes belong to a special group of natural products with a wide range of pharmacological functions. Its basic skeletal structure contains a five-membered ring, a seven-membered ring, two methyl, and one isopropyl groups. Thapsigargin, a major ingredient in *Thapsia garganica*, could inhibit the sarco-endoplasmic reticulum $Ca^{2+}$-ATPase (SERCA) to deplete the intracellular $Ca^{2+}$ pool and induce apoptosis in human hepatoma cells. An X-ray structure of the thapsigargin-SERCA complex provided the foundation for understanding the structural conformation of the complex, as well as the surroundings of the binding site. This additionally provided detailed information for the design of a targeted prodrug with thapsigargin as the active component (Andersen et al. 2015), such as mipsagargin (G202). G202 has completed the phase II clinical trials in the treatment of glioblastoma multiforme and hepatocellular carcinoma, and is expected to enter the market in the near future. (Brennen et al. 2012; Denmeade et al. 2012; Jakobsen et al. 2001; Simonsen et al. 2013). But, to our knowledge, the related review of guaiane-type sesquiterpenes are insufficient since 1990s. Therefore, in this review, we summarize the current understanding of the chemical studies of guaiane-type

✉ Liu-Qiang Zhang
04100217@163.com

✉ Yi-Ming Li
ymlius@163.com

[1] School of Pharmacy, Shanghai University of Traditional Chinese Medicine, 1200 Cailun Road, 201203 Shanghai, China

[2] Shanghai Institute of Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, 201203 Shanghai, China

sesquiterpenes in plants and the progress that has been made in uncovering their pharmacological activities from 1990 to 2018.

## Biogenesis and sources

Plant species reported to contain guaiane-type sesquiterpenes are listed in Table 1 in alphabetical order. Guaiane-type sesquiterpenes are distributed in approximately 70 genera of 30 families, such as Asteraceae, Lamiaceae, Thymelaeaceae, Umbelliferae, and Zingiberaceae. Furthermore, they are the most widely present in ~26 genera of Asteraceae, especially in *Saussurea*, *Artemisia*, and *Inula*. As we all know, mevalonic acid (MVA) pathway is the main biosynthesis pathway of terpenoids, and farnesyl pyrophosphate (FPP) is the precursor of most sesquiterpenes. Through further literature research, it was found that guaiane-type sesquiterpenes were transformed from FPP by two possible mechanisms, the first was free radical mechanism, the second was ionic mechanism. The biosynthetic pathway of the two mechanisms is shown in Fig. 1 (Adekenov 2017; Zurich 1953). More than 50% of guaiane-type sesquiterpenes contains lactone fragments, and the previous studies showed that most of them possessed the better biological activities than guaiane-type sesquiterpenes without lactone ring. There were two possible pathways for the biotransformation of lactones: one is that guaiane-type sesquiterpenes might be oxidized directly to alcohols and acids, then dehydrated to form lactones. The other was germacranolides intermediates, through which guaianolides were mainly converted in Compositae and Umbelliferae, and their biosynthesis was related to cytochrome P450 enzymes (such as CYP71BL1 and CYP71BL2), adequate oxygen and nicotinamide adenine dinucleotide phosphate (NADPH). Their biosynthetic pathway is proposed in Fig. 2 (Adekenov 2017; Barquera-Lozada and Cuevas 2009; Fischer 1990; Simonsen et al. 2013).

## Classifications

This section summarizes the more than 300 guaiane-type sesquiterpenes reported since the 1990s. Their classification and structures are depicted in Figs. 3–10. Guaiane-type sesquiterpenes can be divided into five categories on the basis of their skeleton: guaianolides, tricycle guaiane-type sesquiterpenes, dimers or trimers containing guaiane-type sesquiterpenes mother nuclei, variant guaiane-type sesquiterpenes, other guaiane-type sesquiterpenes. Guaiane-type sesquiterpenes often occurs in oxygenated forms, such as guaiane alcohol, guaiane acid, guaiane ketone, and guaianolide. Of these, guaianolide is the most abundant guaiane-type sesquiterpene, and it can be further classified as 12,6-guaianolide, 12,8-guaianolide, and pseudoguaianolide. The only difference is that the linkage position of Me-15 on C-4 in 12,8-guaianolides whereas on C-5 in pseudoguaianolides. According to C-11 bonding sites, tricycle guaiane-type sesquiterpenes could be divided into 11,1, 11,6, and 11,10-guaiane. they can also be occasionally oxidized to alcohols, ketones, and acids. Several special structures, such as dimers or trimers containing guaiane-type sesquiterpenes mother nuclei and variant guaiane-type sesquiterpenes, have also been reported. These compounds are of interest because several of them possess biological or therapeutic activities, including antitumor, anti-inflammatory, and antibacterial effects.

## Biological activities

Experimental data have shown that guaiane-type sesquiterpenes possess a wide range of biological activities, including cytotoxic, antitumor, anti-inflammatory, antibacterial, and antiviral.

### Cytotoxic and antitumor activities

Several recent studies have reported that guaiane-type sesquiterpenes possess potential anticancer activity through the inhibition of the proliferation of various cancer cells in vitro. Table 2 presents the plant origins of this bioactive guaiane-type sesquiterpenes and their cytotoxic activities. These in vitro data suggest that guaiane-type sesquiterpenes may not only have a broad spectrum but also strong cytotoxic activity, especially in breast cancer, liver cancer, lung cancer, and leukemia cells. Structures with antitumor activities are distributed in 11,10-guaiane, 12,6-guaianolide, 12,8-guaianolide, pseudoguaianolide, dimers or trimers containing guaiane-type sesquiterpenes mother nuclei, and other guaiane-type sesquiterpenes. Most compounds with antineoplastic activity belong to guaianolides, and the acyl diversity at C-8 is the only dissimilarity in compounds **10**–**14**, which is a good opportunity to evaluate the effect of acyl groups on the antiproliferative activity of sesquiterpene derivatives because of the significant difference in their activity. Therefore, the lowest active compounds were isobutanol derivative **12** and acetyl derivative **14**, while compounds **10**, **11** and **13** are the most active guaianolides in this series. The above compounds either have oxygen functional groups, such as **13**, or contain Michael receptors, such as **10**. Compound **11** has both these two particular structures, so its biological activity is the supreme, at least on CCRF-CEM (Formisano et al. 2017).

**Table 1** Plant species including guaiane-type sesquiterpenes in the references from 1990 to 2018

| Family | Genus | Species | Reference |
|---|---|---|---|
| Alismataceae | *Alisma* | *Alisma orientale* | (Feng et al. 2014; Masullo et al. 2015; Matsuda et al. 1999; Tian et al. 2014; Yoshikawa et al. 1993) |
| Annonaceae | *Oxandra* | *Oxandra sessiliflora* | (De Sousa et al. 2014) |
| | *Artabotrys* | *Artabotrys stenopetalus* | (Fleischer et al. 1997) |
| | *Xylopia* | *Xylopia aromatica* | (Maktins et al. 1998) |
| | | *Xylopia vielana* | (Xie et al. 2018a; Xie et al. 2018b; Xie et al. 2018c) |
| Araliaceae | *Schefflera* | *Schefflera venulosa* | (Peng et al. 2015) |
| Asclepiadaceae | *Secamone* | *Secamone lanceolata* | (Yang et al. 2018) |
| Asteraceae | *Saussurea* | *Saussurea deltoidea* | (Xu et al. 2012b) |
| | | *Saussurea laniceps* | (Wang et al. 2010a) |
| | | *Saussurea lappa* | (Yang et al. 2016c) |
| | | *Saussurea jxponica* | (Jia et al. 1991) |
| | | *Saussurea involucrata* | (Xiao et al. 2011) |
| | *Ligularia* | *Ligularia virgaurea* | (Saito et al. 2013) |
| | | *Ligularia duciformis* | (Gao and Jia 1999) |
| | *Lactuca* | *Lactuca sativa var. anagustata* | (Guarrera and Savo 2016; Han et al. 2010; Zidorn 2008) |
| | | *Lactuca tatarica* | (Wang et al. 2010b) |
| | | *Lactuca serriola* | (Marco et al. 1992) |
| Asteraceae | | *Lactuca virosa* | (Stojakowska et al. 1994) |
| | *Ajania* | *Ajania przewalskii* | (Zhu et al. 2010) |
| | *Senecio* | *Senecio scandens* | (Zhao et al. 2015) |
| | *Eupatorium* | *Eupatorium fortunei* | (Adekenov 2017; Chen et al. 2013) |
| | *Artemisia* | *Artemisia alba* | (Todorova et al. 2015) |
| | | *Artemisia roxbughiana* | (Phan et al. 2012) |
| | | *Artemisia austro-yunnanensis* | (Chi et al. 2016) |
| | | *Artemisia anomala* | (Zan et al. 2012) |
| | | *Artemisia absinthium* | (Safarova and Serkerov 1997) |
| | | *Artemisia caruifolia* | (Ma et al. 2000) |
| | | *Artemisia glabella* | (Lone et al. 2015) |
| | *Centaurea* | *Centaurea drabifolia* | (Formisano et al. 2017) |
| | | *Centaurea scoparia* | (Bruno et al. 2013; Youssef 1998) |
| | *Moscharia* | *Moscharia pinnatifida* | (Singh and Suri 1990) |
| | *Scorzonera* | *Scorzonera divaricata* | (Wu et al. 2018; Yang et al. 2016d) |
| | *Atractylodes* | *Atractylodes lancea* | (Kamauchi et al. 2015; Wang et al. 2008) |
| | *Inula* | *Inula japonica* | (Wu et al. 2016; Zhu et al. 2013) |
| | | *Inula sericophylla* | (Cheng et al. 2012) |
| | | *Inula lineariifolia* | (Qin et al. 2013) |
| | | *Inula falconeri* | (Cheng et al. 2011) |
| | *Tanacetum* | *Tanacetum oshanahanii* | (Triana et al. 2013) |
| | *Helianthus* | *Helianthus annuus* | (Joel et al. 2011) |
| | *Perezia* | *Perezia recurvata* | (Gallardo et al. 2011) |
| | *Launaea* | *Launaea arborescens* | (Bitam et al. 2008) |
| | *Tithonia* | *Tithonia diversifolia* | (Pantoja Pulido et al. 2017) |
| | *Cichorium* | *Cichorium intybus* | (Deng et al. 2001) |
| | *Mulgedium* | *Mulgedium tatarica* | (Ren et al. 2005) |
| Asteraceae | *Carpesium* | *Carpesium abrotanoides* | (Wang et al. 2018b; Zhang et al. 2015) |
| | *Achillea* | *A. clypeolata* | (Mohammadhosseini et al. 2017) |

**Table 1** (continued)

| Family | Genus | Species | Reference |
|---|---|---|---|
| | *Arctotis* | *Arctotis arctotoides* | (Saleh-E-In and Staden 2018) |
| | *Tragopogon* | *T. porrifolius* | (Asadi-Samani et al. 2015) |
| | *Taraxacum* | *Taraxacum officinale* | (Kisiel and Barszcz 2000) |
| | *Haplopappus* | *Haplopappus foliosus* | (Labbb et al. 1998) |
| | *Ixeris* | *Ixeris sonchifolia* | (Warashin et al. 1990) |
| Burseraceae | *Commiphora* | *Commiphora opobalsamum* | (Yang and Shi 2012) |
| | | *Commiphora quidotti* | (Fraga 1999) |
| | | *Commiphora myrrha* | (Shen et al. 2012; Xu et al. 2012a) |
| Caprifoliaceae | *Viburnum* | *Viburnum awabuki* | (Fukuyam et al. 1996) |
| Chloranthaceae | *Chloranthus* | *Chloranthus japonicus* | (Zhuo et al. 2017) |
| | | *Chloranthus multistachys* | (Liu et al. 2013) |
| | *Hedyosmum* | *Hedyosmum brasiliense* | (Amoah et al. 2015) |
| Cupressaceae | *Callitris* | *Callitris sulcata* | (Hnawia et al. 2008) |
| | | *Callitris pancheri* | (Raharivelomanan et al. 1996) |
| Cyperaceae | *Cyperus* | *Cyperus rotundus* | (Xu et al. 2015) |
| Frullaniaceae | *Frullania* | *Frullania tamarisci* | (Asakawa et al. 2013) |
| Geraniaceae | *Pelargonium* | *Pelargonium graveolens* | (Zhang et al. 1996) |
| Lamiaceae | *Pogostemon* | *Pogostemon cablin* | (Du et al. 1998; Guan et al. 1992; Li et al. 2013a; Liu et al. 2015; Luo et al. 1999; Rakotonirainy et al. 1997; Swamy and Sinniah 2015; Zhu et al. 2017) |
| | *Scutellaria* | *Scutellaria baicalensis* | (Yang and Zhang 1999) |
| | *Salvia* | *Salvia mirzayanii* | (Ziaei et al. 2015) |
| | | *Salvia plebeia* | (Zou et al. 2018) |
| | *Teucrium* | *Teucrium viscidum* | (Hao et al. 2013) |
| | | *Teucrium leucockidum* | (Ahmed et al. 1996) |
| | *Thapsia* | *Thapsia villosa* | (Lemmich et al. 1991) |
| Lauraceae | *Laurus* | *Laurus nobilis* | (Pacifico et al. 2013) |
| Lauraceae | *Litsea* | *Litsea resinosa* | (Wang et al. 2016) |
| Leguminosae | *Caesalpinia* | *Caesalpinia spinosa* | (Mu et al. 2016) |
| Meliaceae | *Aglaia* | *Aglaia odorata var. microphyllina* | (Liu et al. 2014b) |
| Myrtaceae | *Eugenia* | *Eugenia candolleana* | (Nakamura et al. 2010) |
| Oleaceae | *Syringa* | *Syringa pinnatifolia* | (Ao et al. 2012) |
| Pittosporaceae | *Pittosporum* | *Pittosporum undulatum* | (Mendes et al. 2013) |
| Plexauridae | *Echinogorgia* | *Echinogorgia sassapo reticulata* | (Xue et al. 2014) |
| Porellaceae | *Porella* | *Porella acutifolia subsp. tosana* | (Li et al. 2013b) |
| | | *Porella swartziana* | (Tori et al. 1996) |
| Rubiaceae | *Gardenia* | *Gardenia jasminoides* | (Li and Wang 2016) |
| | | *Gardenia sootepensis* | (Rukachaisiriku et al. 1998) |
| Rutaceae | *Dictamnus* | *Dictamnus dasycarpus* | (Takeuchi et al. 1993) |
| Thymelaeaceae | *Daphne* | *Daphne aurantiaca* | (Huang et al. 2017) |
| | | *Daphne tangutica* | (Yin et al. 2018) |
| | *Stellera* | *Stellera chamaejasme* | (Liu et al. 2014a) |
| | *Gyrinops* | *Gyrinops salicifolia* | (Shao et al. 2016) |
| | *Aquilaria* | *Aquilaria agallocha* | (Ishihara et al. 1991) |
| | | *Aquilaria sinensis* | (Hashim et al. 2016; Ishihara et al. 1993; Yang et al. 2016a; Yang et al. 2016b) |
| Ulvaceae | *Ulva* | *Ulva fasciata* | (Chakraborty et al. 2010; Gutierrez-Rodriguez et al. 2018) |

**Table 1** (continued)

| Family | Genus | Species | Reference |
|---|---|---|---|
| Umbelliferae | *Ferula* | *Ferula diversivittata* | (Iranshahi et al. 2008) |
| | *Torilis* | *Torilis japonica* | (Chen et al. 2011; Endale et al. 2013; Kitajima et al. 1998) |
| | *Daucus* | *Daucus carota* | (Fu et al. 2010a; Fu et al. 2010b) |
| | *Notopterygium* | *Notopterygium incisum* | (Azietaku et al. 2017) |
| | *Peucedanum* | *Peucedanum cervariifolium* | (Sarkhail 2014) |
| Ulmaceae | *Ulmus* | *Ulmus davidiana* | (Kim et al. 2007) |
| Urticaceae | *Oreocnide* | *Oreocnide frutescens* | (Zhang et al. 2010) |
| Valerianaceae | *Nurdostuchys* | *Nurdostuchys chinensis* | (Takaya et al. 1998; Takaya et al. 2000) |
| Xeniidae | *Xenia* | *Xenia stellifera* | (Phan et al. 2018) |
| Zingiberaceae | *Curcuma* | *Curcuma aeruginosa* | (Balaji and Chempakam 2010; Suphrom et al. 2012) |
| | | *Curcuma aromatica* | (An et al. 2016; Chen et al. 2014b; Lu et al. 2012) |
| | | *Curcuma kwangsiensis* | (Wang et al. 2018a; Xiang et al. 2018) |
| | | *Curcuma wenyujin* | (Dong et al. 2013; Xia et al. 2015; Zhou et al. 2017) |
| | | *Curcuma heyneana* | (Cho et al. 2009) |
| | | *Curcuma phaeocaulis* | (Chen et al. 2014a) |
| | | *Curcuma longa* | (Li et al. 2010) |

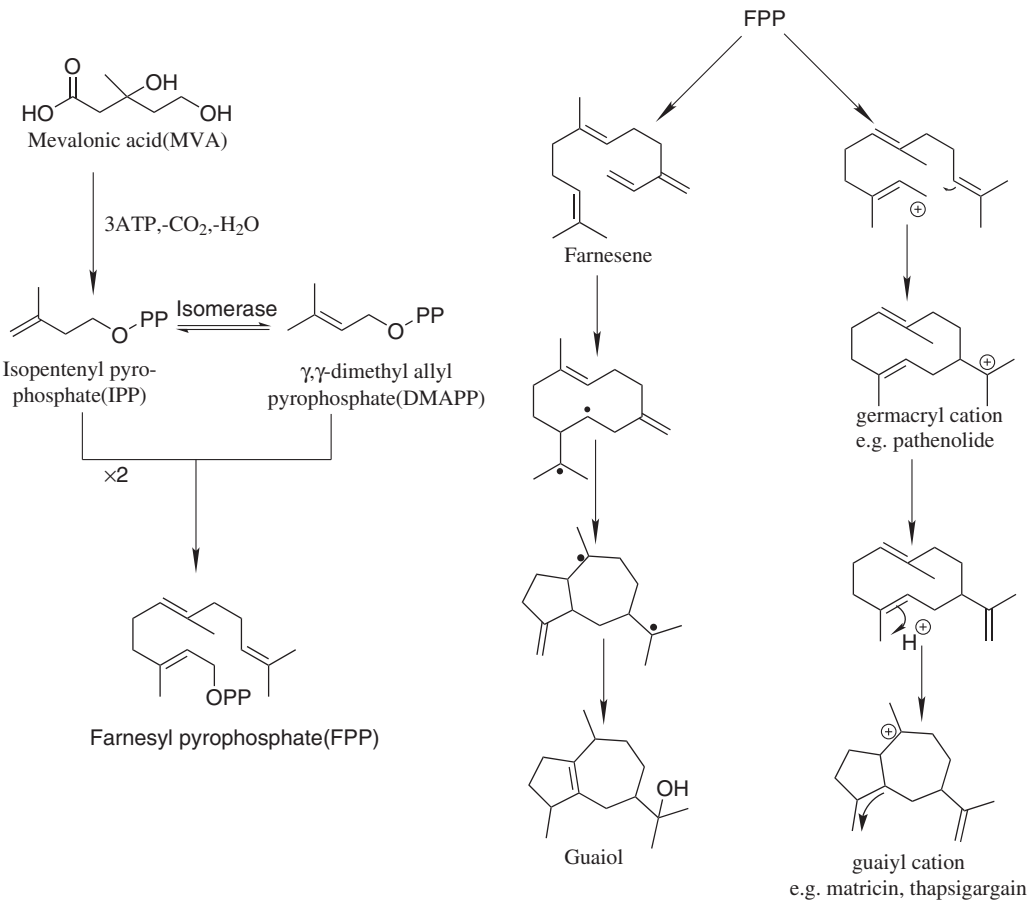



**Fig. 1** On the left is the MVA pathway of FPP, and the right one are two mechanisms of transformation of guaiane-type sesquiterpenes. Pathway one (left): radical mechanisms in the biogenesis of sesquiterpenes, pathway two (right): ionic mechanisms in the biogenesis of sesquiterpenes

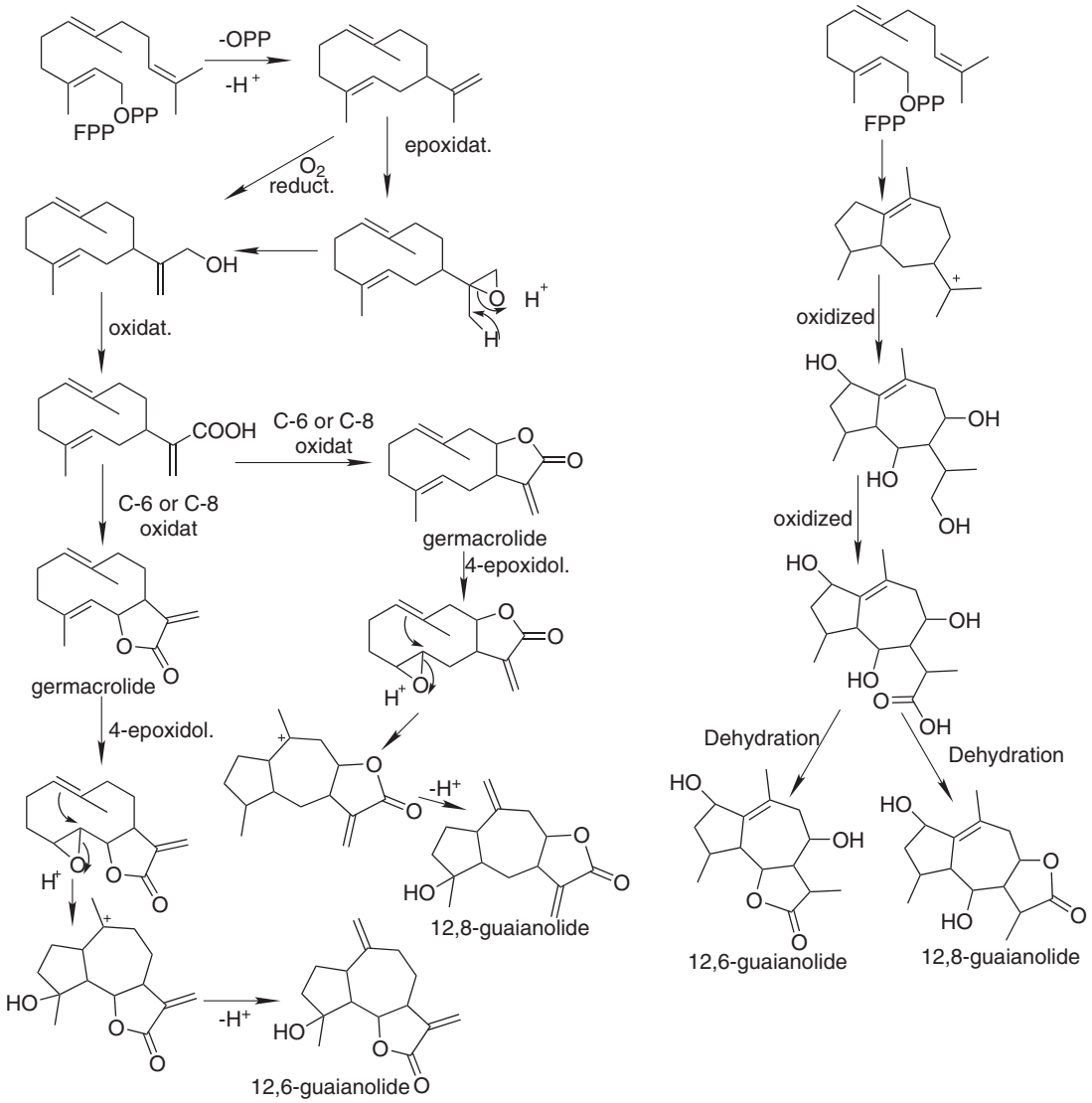



**Fig. 2** The biosynthesis pathway of guaianolide. The left guaianolide is transformed by germacranolides intermediates, and the right guaianolide is formed directly by oxidation and dehydration

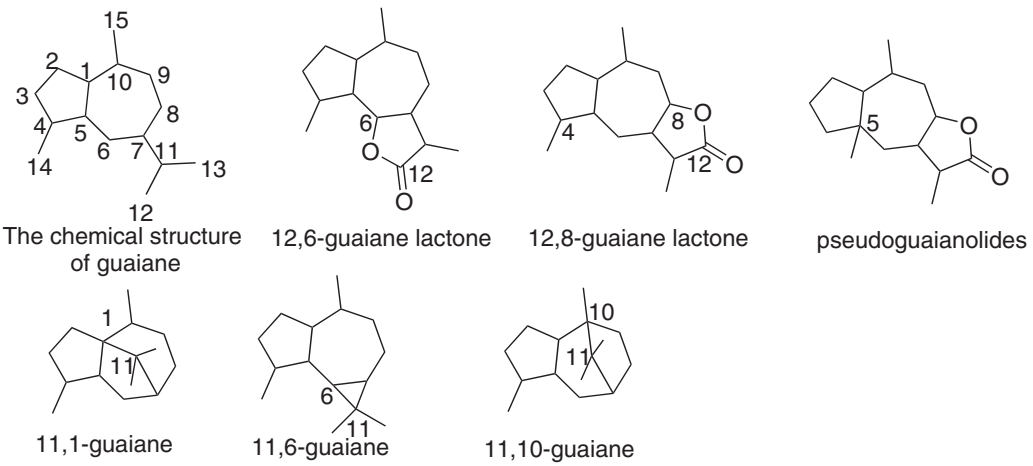



**Fig. 3** The basic skeletal structure of guaiane-type sesquiterpenes from natural material

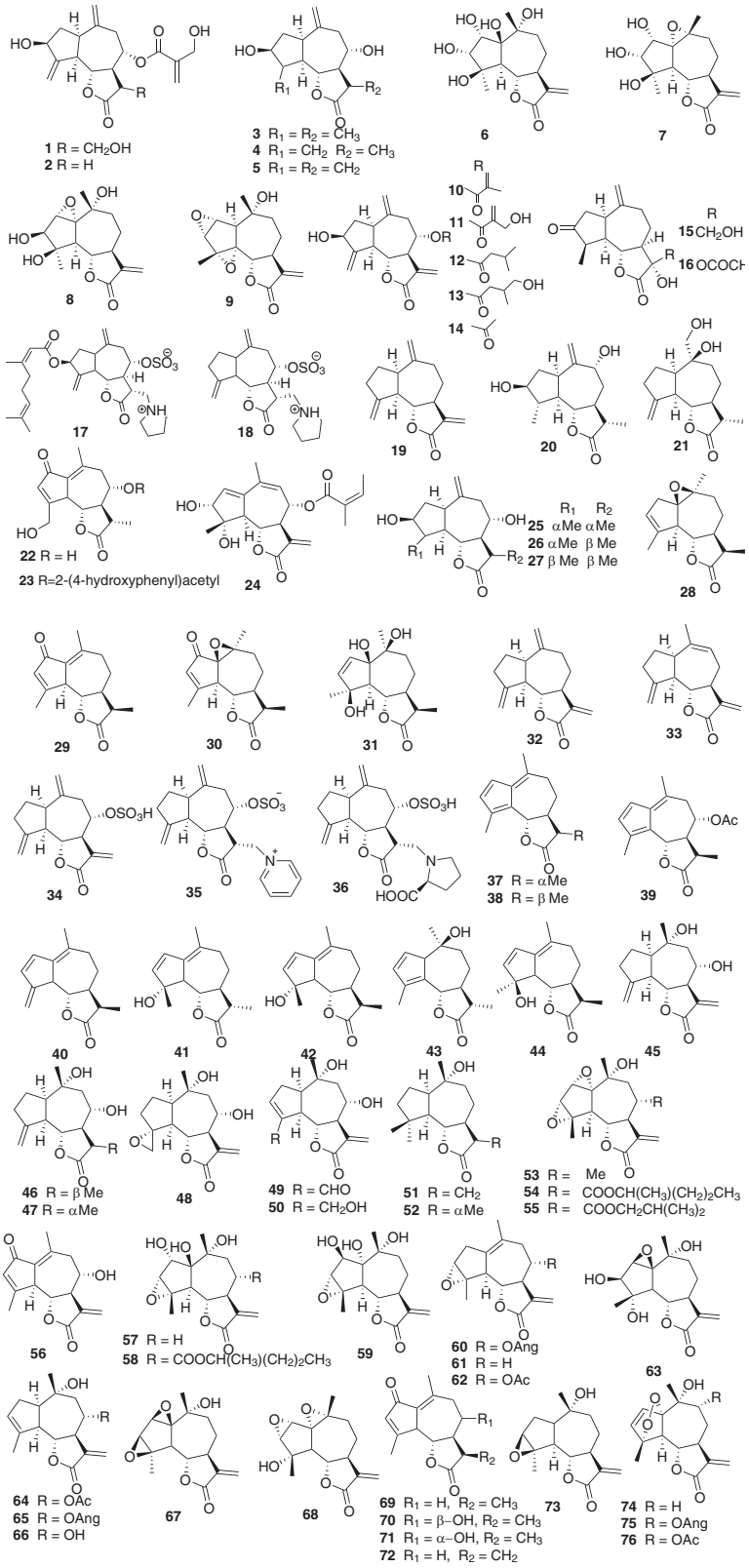
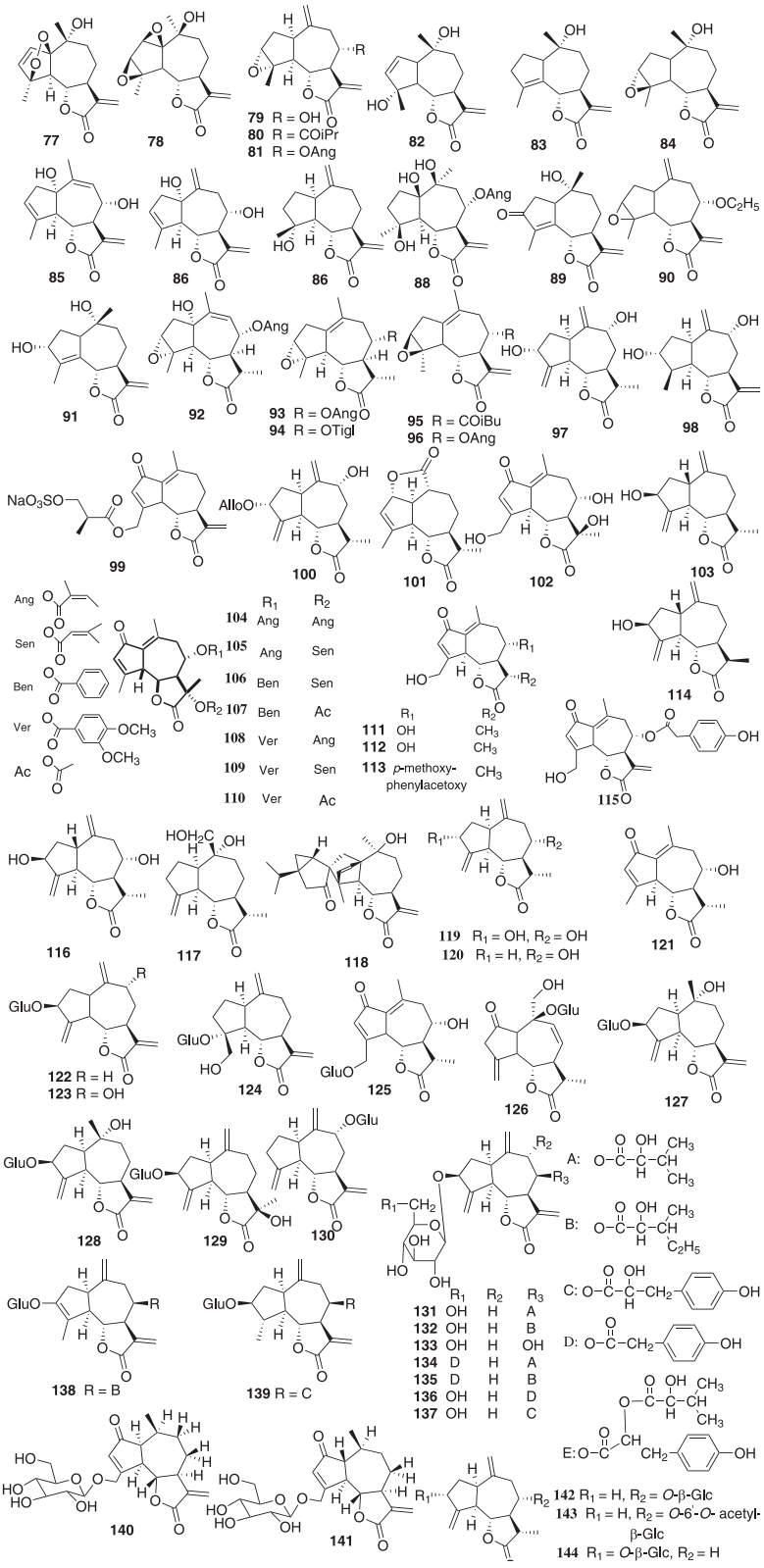



**Fig. 4** The chemical structures of 12,6-guaianolides (**1**–**144**) from natural material (23 of them are 12,6-guaianolide glycosides.)

**Fig. 4** (Continued)



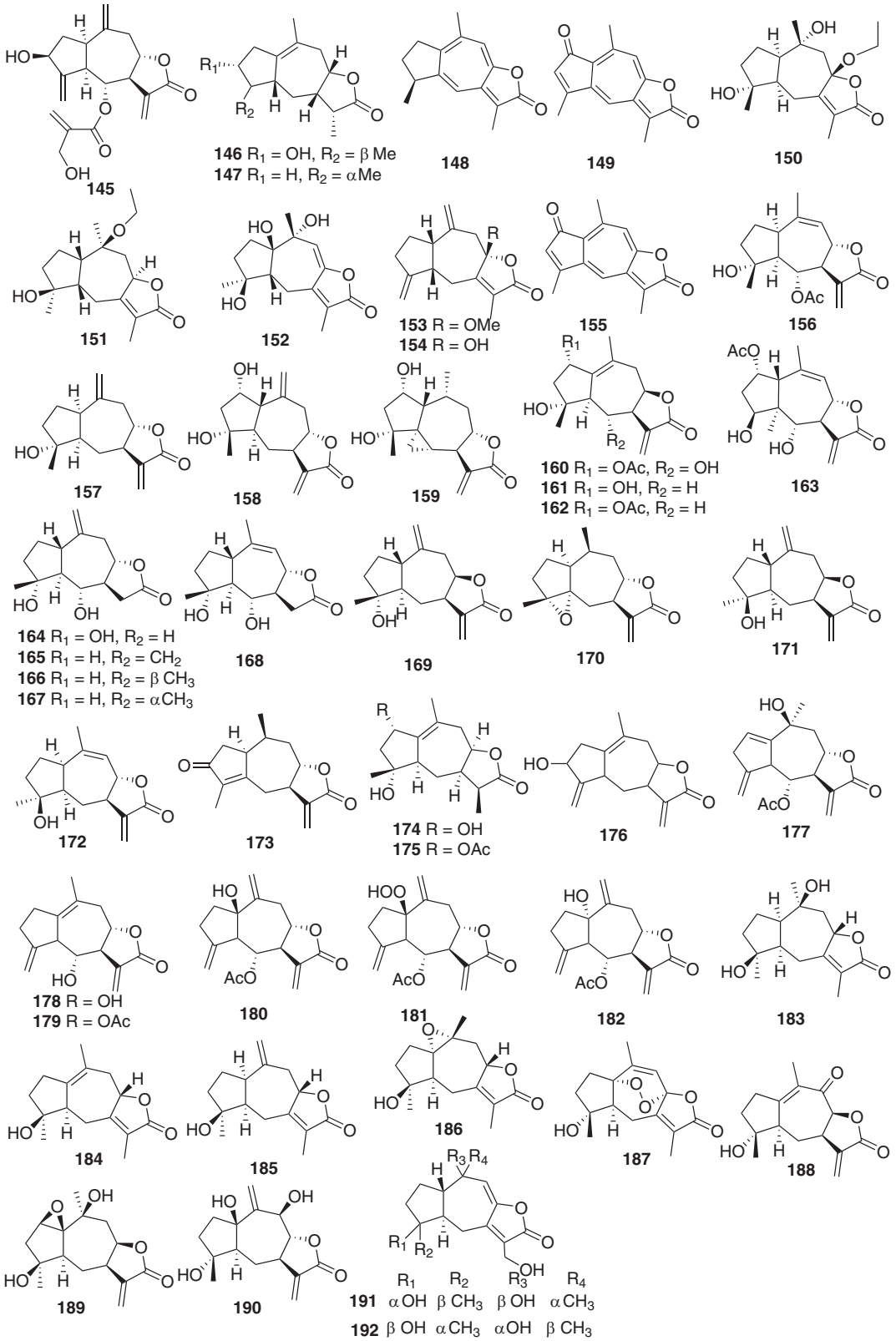



**Fig. 5** The chemical structures of 12,8-guaianolides **(145–192)** from natural material

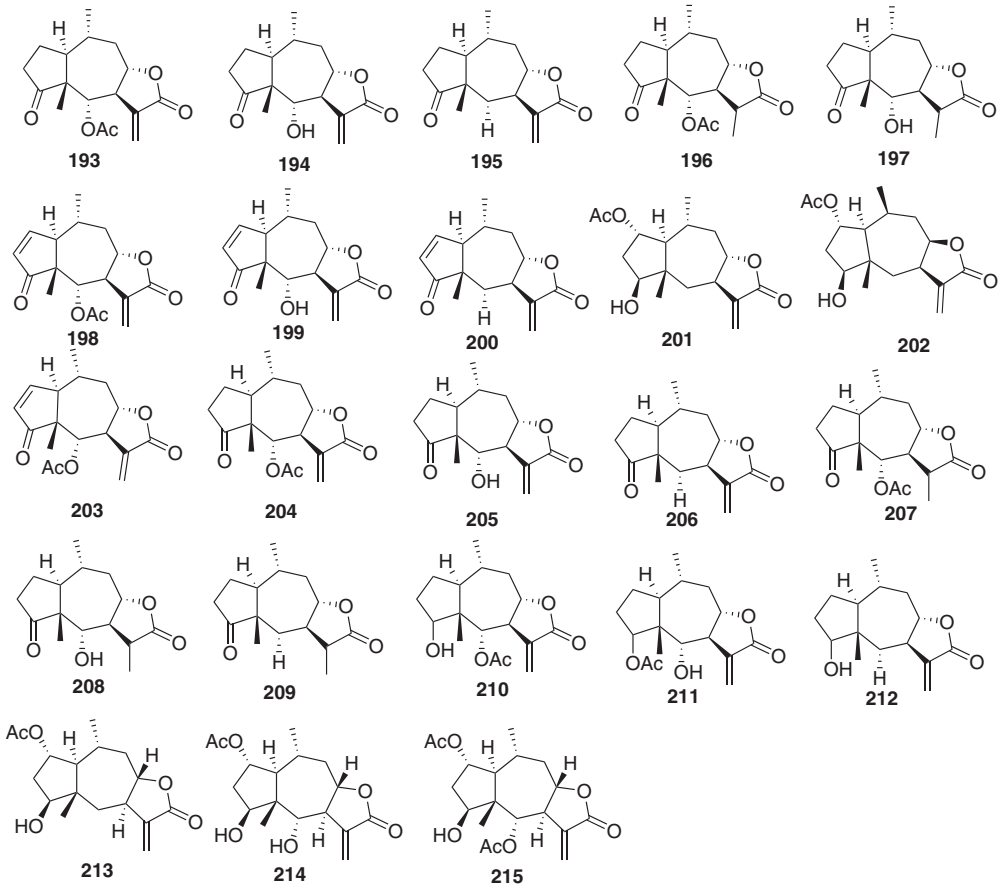



**Fig. 6** The chemical structures of pseudoguaianolides (**193**–**215**) from natural material (the only difference is that the linkage position of Me-15 on C-4 in 12,8- guaianolides whereas on C-5 in pseudoguaianolides.)

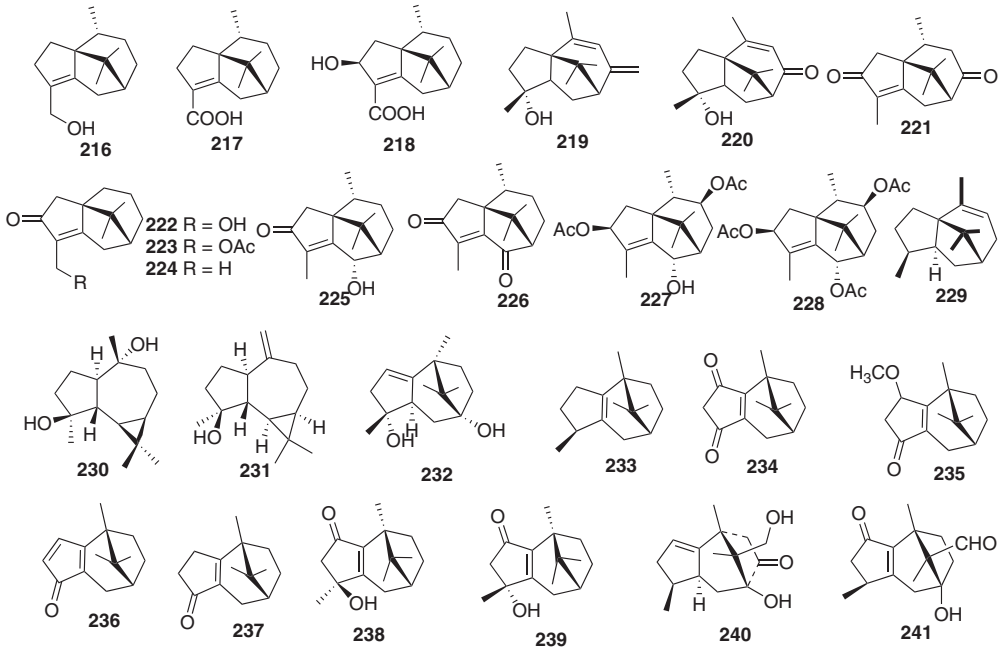



**Fig. 7** The chemical structures of tricycle guaiane-type sesquiterpenes (**216**–**241**) from natural material (according to their carbon skeleton links, compounds **216**–**229** were 11,1-guaianes, compounds **230** and **231** were 11,6 guaianes, and compounds **232**–**241** were 11,10 guaianes.)

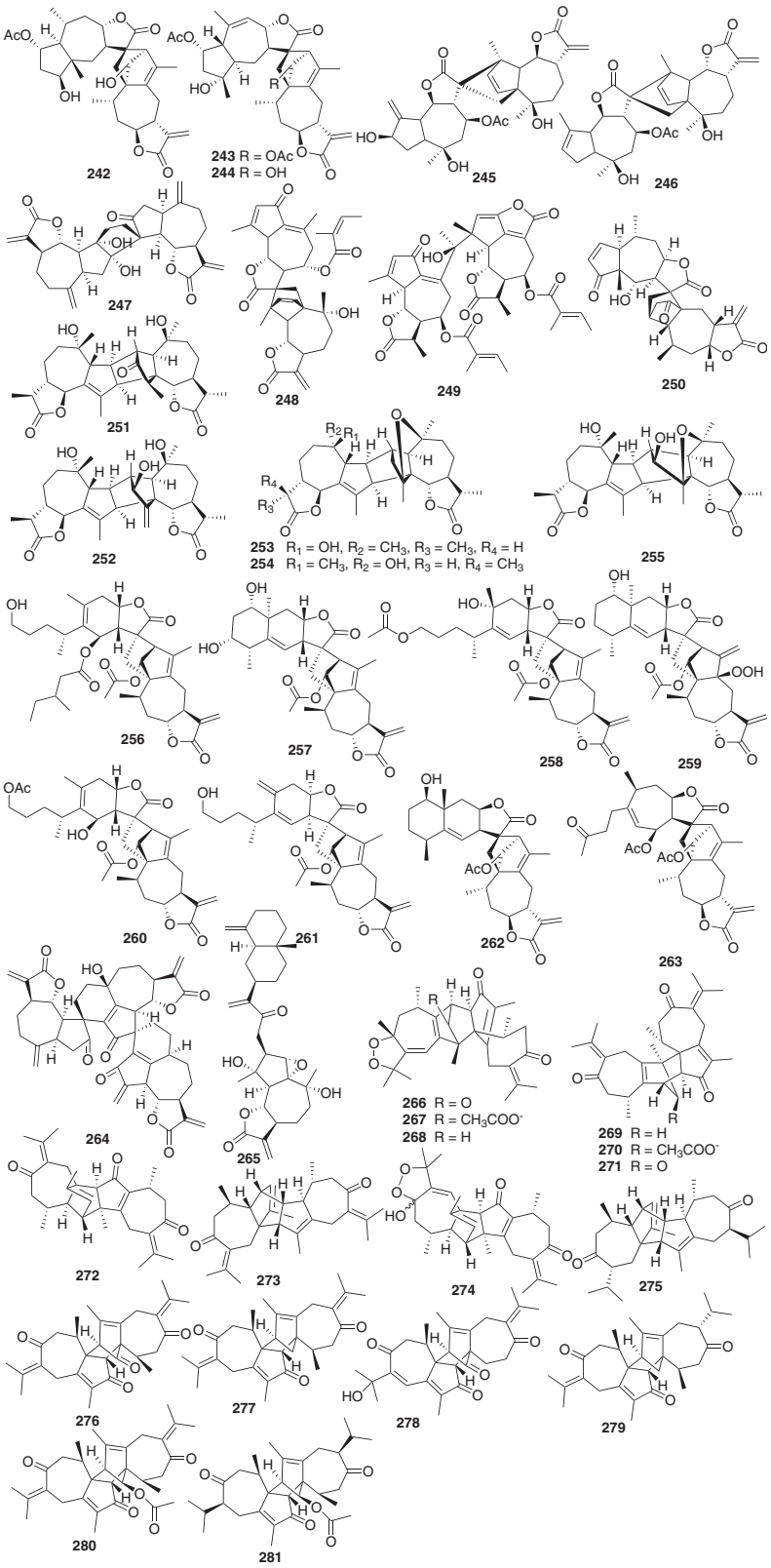



**Fig. 8** The chemical structures of dimers or trimers containing guaiane-type sesquiterpenes mother nuclei from natural material (Compounds **242**–**255** and **266**–**281** are guaiane dimers, **263** are guaiane trimers, and the rest are dimers with a guaiane mother-core structure.)

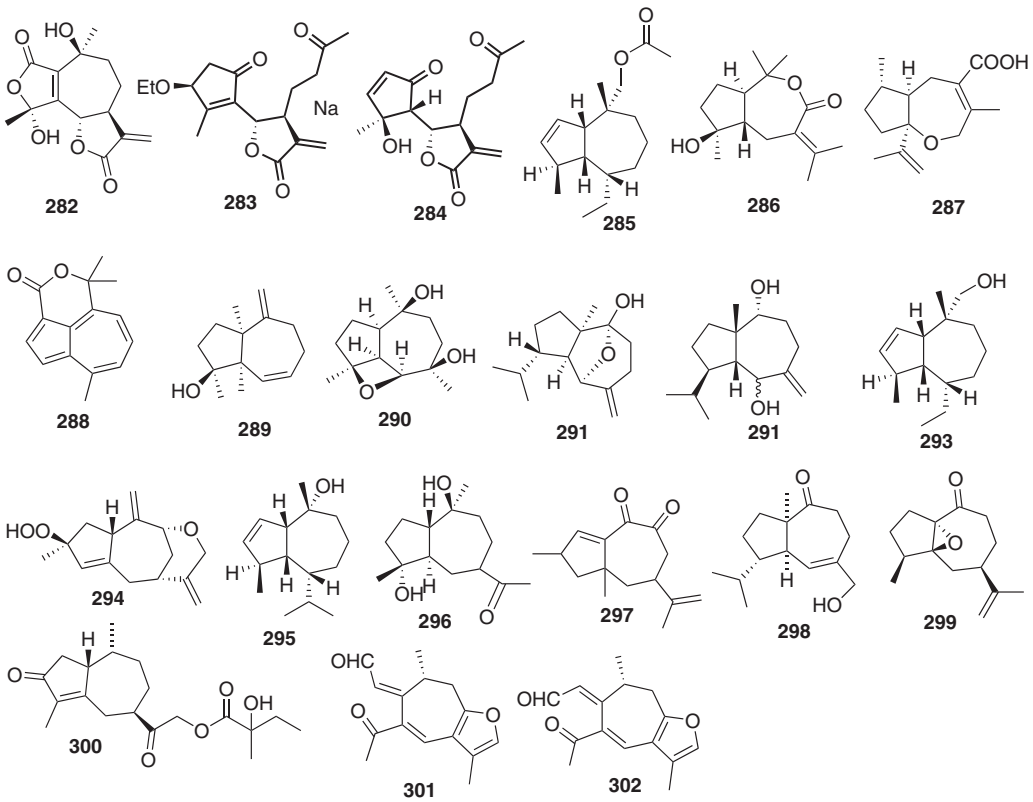



**Fig. 9** The chemical structures of variant guaiane-type sesquiterpenes (**282**–**302**) from natural material

## Anti-inflammatory activity

Inflammation is a cell's response to injury caused by noxious physical or chemical stimuli; it is a key component of multiple pathologies, such as arthritis, asthma, multiple sclerosis, inflammatory bowel disease, and atherosclerosis (Cho et al. 2009). Nitric oxide (NO) is a well-known proinflammatory mediator in the pathogenesis of inflammation. Numerous studies have reported the inhibitory effects of NO on guaiane sesquiterpenes. Compounds **311**, **321**, **327**, **340**, **7–9**, **150**, **164–173**, **204–212**, **393**, **134**, **366–368**, **248**, and **256–261** all had their NO production inhibited in lipopolysaccharide (LPS)-activated mouse macrophages; their $IC_{50}$ data are listed in Table 3; compound **204** separated from *Inula falconeri* exhibited the highest potency ($IC_{50} = 0.07$ μM; Cheng et al. 2011). Likewise, compounds **186**, **247–249**, and **264** isolated from *A. macrocephala*, *Ainsliaea fulvioides*, *Eupatorium perfoliatum*, and *Helenium microcephalum* effectively regulated the expression of tumor necrosis factor (TNF) - $\alpha$, interleukin (IL) $-1\beta$, IL-6, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) mRNAs in LPS-induced RAW264.7 cells (Qin et al. 2017).

A structural activity analysis revealed that compounds with anti-inflammatory activity were mainly distributed in 12,8-guaianolides, pseudoguaianolides, and guaiane polymers, most of which contained 12,8-lactone rings. Therefore, we speculated that their lactone rings are key to their activity, further research is necessary to reach a definite conclusion. Among them, compounds **164**, **165**, **170**, **204**, **206**, and **210** showed better NO inhibitory activity and their $IC_{50}$ values were <1 μM. The compared chemical structure between **207** and **204**, between **208** and **205**, between **209** and **206**, respectively, it was found that the deletion of an $\alpha,\beta$-unsaturated carbonyl group reduced the inhibitory activities. Through comparing pseudoguaiacolide **204**–**205** and **207**–**208**, it showed that the acetylation of the hydroxyl groups usually enhanced the lipophilicity of the compounds, which was conducive to better penetrating the cell membrane and enhancing the inhibition of NO production. On the contrary, the inhibitory activity of **205** was 5 times weaker than **206** lacking the hydroxyl in C-6, similarily **208** was two times weaker than **209**. The above results demonstrated that the introduced hydroxyl might reduce the permeability of the cell membrane and its anti-inflammatory activity. Besides, the position of hydroxyl groups may play a more important role than the number of hydroxyl groups, because compounds **164** and **165** each contain two hydroxyl groups with $IC_{50}$ values of 0.29 and 0.13 μM, respectively.

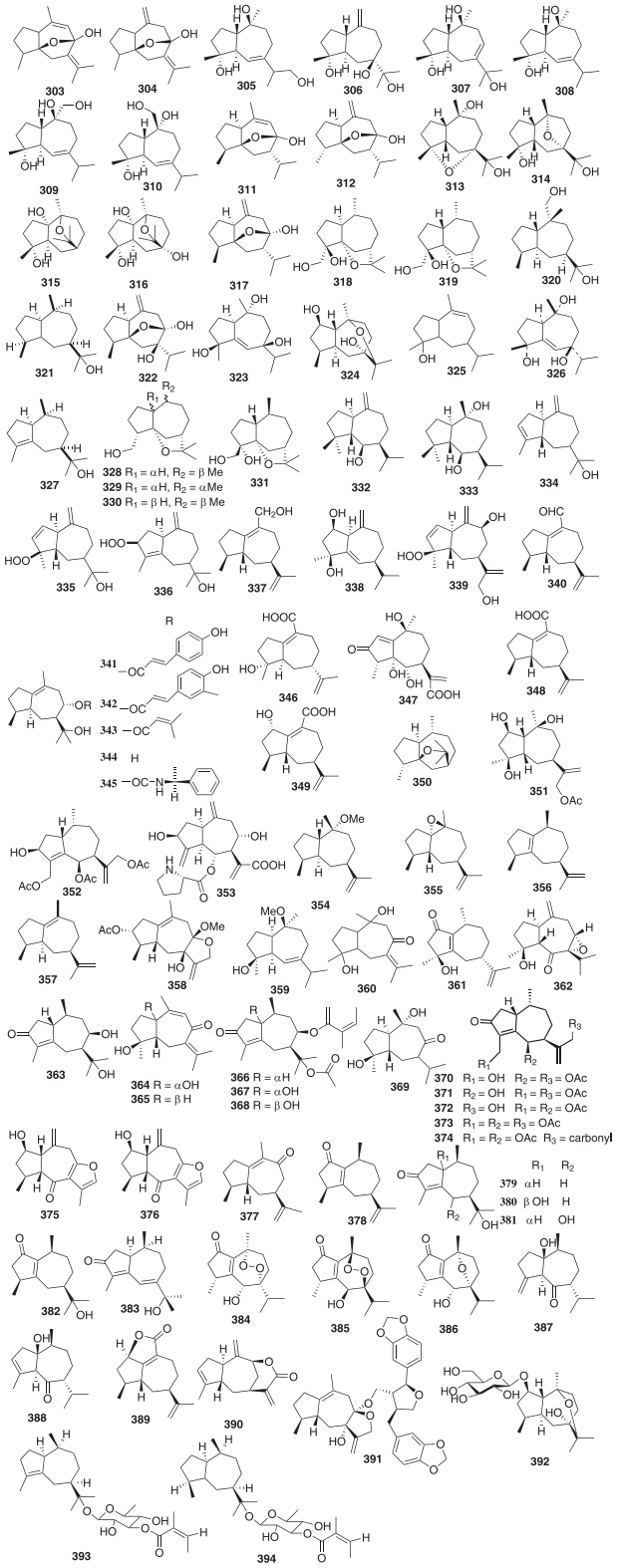


**Fig. 10** The chemical structures of other guaiane-type sesquiterpenes (**303**–**394**) from natural material

Moreover, the cyclic olefinic bond between C-9 and C-10 might be an important group for inhibiting NO production activity, because the inhibitory effects between **164** and **165** were significantly different.(Cheng et al. 2011).

## Antibacterial activity and antiviral activity

Antibacterial and antiviral activities are common in these compounds. Compound **7** isolated from *Scorzonera divaricata* exerted antibacterial activity against *C. Perfringens* and *E. coli* with minimal inhibitory concentrations (MICs) of 25 and 50 μM, respectively (Wu et al. 2018). Compounds **328**, **329**, and **284** isolated from *Ulva fasciata* exerted antibacterial activity against *Vibrio parahaemolyticus* American Type Culture Collection (ATCC) 17809, *V. harveyi* Microbial Type Culture Collection (MTCC) 3438, and *V. vulnificus* MTCC 1146, respectively. Of these, compound **284** exerted the most antibacterial activity, with MICs of 25, 30, and 25 μg/mL on these bacteria, respectively (Chakraborty et al. 2010). Compounds **104**, **107**, **109**, and **110** separated from *Ferula diversivittata* similarly showed antimicrobial activity against *E. coli* (ATCC8739), *Staphylococcus aureus* (ATCC29737), and *Aspergillus niger* (ATCC1624), and compound **109** exhibited the strongest antibacterial activity about these bacteria (MIC: 80, 80, 80 μM; Iranshahi et al. 2008). In addition, compounds **325** and **297** separated from *Syringa pinnatifolia* exhibited antimicrobial activity (Ao et al. 2012). Observing the structure is of interest as these compounds are not as anti-inflammatory as they appear: 12,6-guaianolide had the strongest antimicrobial activity, whereas 12,8-type lactones had nearly no reported antimicrobial activity.

Compound **317**, a natural product from *Curcuma aromatica*, showed anti-influenza virus activities, with estimated $IC_{50}$ values of 11.08 ± 1.74 μM (An et al. 2016; Chen et al. 2014b; Lu et al. 2012). Similarly, compounds **322**, **187**, **364**, **365**, **369**, and **275** isolated from *Curcuma wenyujin* had anti-influenza virus activities ($IC_{50}$: 9.18 ± 0.46, 6.80 ± 0.13, 22.21 ± 2.01, 13.27 ± 1.46, 15.95 ± 0.69, and 12.84 ± 0.73 μM; Dong et al. 2013; Xia et al. 2015; Zhou et al. 2017). Compounds **216**–**226** isolated from *Cyperus rotundus* had anti- hepatitis B virus (HBV) activities, and compound **217** had the strongest activity, with $IC_{50}$ values as follows: hepatitis B surface antigen (HBsAg): 77.2 ± 13.0 μM, hepatitis B e antigen (HBeAg): 1210.2 ± 101.1 μM, HBV DNA: 74.7 ± 7.2 μM (Xu et al. 2015). The 11,1-guaiane exert some anti-HBV activities, but some modifications are necessary to enhance its activity.

## Other biological activities

Per several reports, compounds **220**, **238**, **239**, and **361** produced from *Pogostemon cablin* have reduced the

**Table 2** Cytotoxic activities of guaiane-type sesquiterpenes from natural material

| Compounds | Plant origin | Cancer cell lines | $IC_{50}$/μM | Ref. |
|---|---|---|---|---|
| **4** | *Saussurea deltoidea* | SMMC-7721 | 24.49 | (Xu et al. 2012b) |
| | | A549 | 18.83 | |
| | | Hela | 5.28 | |
| **5** | | SMMC-7721 | 36.10 | |
| | | Hela | 17.99 | |
| **145** | | SMMC-7721 | 3.55 | |
| | | A549 | 15.46 | |
| | | Hela | 2.69 | |
| **305** | *Aglaia odorata var. microphyllina* | SGC-7901 | 40 | (Liu et al. 2014b) |
| **308** | | SGC-7901 | 38 | |
| **296** | | SGC-7901 | 38.8 | |
| **10** | *Centaurea drabifolia* | CCRF-CEM | 0.83 ± 0.20 | (Formisano et al. 2017) |
| | | CEM/ADR5000 | 1.26 ± 0.179 | |
| **11** | | CCRF-CEM | 0.47 ± 0.07 | |
| | | CEM/ADR5000 | 1.77 ± 0.654 | |
| **12** | | CCRF-CEM | 4.73 ± 0.04 | |
| | | CEM/ADR5000 | 7.08 ± 1.18 | |
| **13** | | CCRF-CEM | 1.65 ± 0.06 | |
| | | CEM/ADR5000 | 3.45 ± 0.36 | |
| **14** | | CCRF-CEM | 25.3 ± 2.59 | |
| | | CEM/ADR5000 | 37.23 ± 4.63 | |
| **15** | | CCRF-CEM | 5.94 ± 0.80 | |
| **16** | | CCRF-CEM | 24.7 ± 0.44 | |
| | | CEM/ADR5000 | 58.18 ± 6.16 | |
| | | HepG2 | 4.21 ± 0.56 | |
| **18** | *Scorzonera divaricata* | K562 | 6.53 ± 0.80 | (Wu et al. 2018) |
| | | HeLa | 8.15 ± 0.36 | |
| **19** | *Saussurea lappa* | HeLa | 12.00 | (Yang et al. 2016c) |
| **158** | *Inula linearifolia* | MCF-7 | 13.7 ± 0.6 | (Qin et al. 2013) |
| | | MDA-MB-231 | 21.1 ± 1.7 | |
| **162** | | MCF-7 | 15.5 ± 0.9 | |
| | | MDA-MB-231 | 25.8 ± 2.1 | |
| **163** | | MCF-7 | 6.2 ± 0.3 | |
| | | MDA-MB-231 | 11.4 ± 0.5 | |
| **202** | | MCF-7 | 6.7 ± 0.5 | |
| | | MDA-MB-231 | 12.9 ± 0.9 | |
| **203** | | MCF-7 | 2.1 ± 0.3 | |
| | | MDA-MB-231 | 2.3 ± 0.1 | |
| | | MCF-10A | 26.0 ± 1.2 | |
| **242** | | MCF-7 | 1.6 ± 0.1 | |
| | | MDA-MB-231 | 2.8 ± 0.2 | |
| | | MCF-10A | 27.9 ± 2.3 | |
| **243** | | MCF-7 | 3.4 ± 0.2 | |
| | | MDA-MB-231 | 10.7 ± 0.7 | |
| **244** | | MCF-7 | 7.8 ± 0.5 | |
| | | MDA-MB-231 | 16.5 ± 1.3 | |
| **323** | *Commiphora opobalsamum* | HeLa | 15.4 | (Yang and Shi 2012) |

**Table 2** (continued)

| Compounds | Plant origin | Cancer cell lines | $IC_{50}$/μM | Ref. |
|---|---|---|---|---|
| | | HepG2 | 8.7 | |
| **213** | *Inula japonica* | HL-60 | 3.67 | (Wu et al. 2016) |
| | | SMMC-7721 | 2.48 | |
| | | A-549 | 3.15 | |
| | | MCF-7 | 2.44 | |
| | | SW-480 | 1.75 | |
| **214** | | HL-60 | 10.25 | |
| | | SMMC-7721 | 3.42 | |
| | | A-549 | 3.82 | |
| | | MCF-7 | 4.15 | |
| | | SW-480 | 2.43 | |
| **215** | | HL-60 | 4.28 | |
| | | SMMC-7721 | 1.75 | |
| | | A-549 | 1.57 | |
| | | MCF-7 | 3.32 | |
| | | SW-480 | 0.97 | |
| **35** | *Scorzonera divaricata* | HeLa | 220.2 ± 11.8 | (Yang et al. 2016d) |
| | | HL-60 | 127.2 ± 6.1 | |
| | | SMMC-7721 | 250.3 ± 18.6 | |
| **36** | | HeLa | 144.2 ± 10.1 | |
| | | HL60 | 91.9 ± 6.8 | |
| | | HepG2 | 212.7 ± 11.8 | |
| | | SMMC-7721 | 249.2 ± 20.0 | |
| **240** | *Stellera chamaejasme* | A549 cells | 1.951 | (Liu et al. 2014a) |
| **103** | *Saussurea involucrata* | A549 cells | 0.01 ± 0.12 | (Xiao et al. 2011) |
| **114** | | A549 cells | 2.89 ± 0.11 | |
| **115** | *Mulgedium tatarica* | KB cells | 20 | (Ren et al. 2005) |
| | | Bel 7402 cells | 17 | |

damage induced by D-galactosamine (D-GalN) on human liver (HL) −7702 cells by 33.0% ± 0.026, 40.5% ± 0.043, 32.4% ± 0.036, 32.3% ± 0.016 at 10 μM (Li et al. 2013a; Zhu et al. 2017). Compound **314** isolated from *Chloranthus japonicus* had inhibitory effects on memory impairment (Amoah et al. 2015; Mu et al. 2016). At 50 μg/mL, compounds **146–149** separated from *Gyrinops salicifolia* exhibited acetylcholinesterase (AChE) inhibitory activity and the inhibition rates were 35.3 ± 1.2, 21.1 ± 1.9, 46.2 ± 0.9, and 54.2 ± 1.4%, respectively (Shao et al. 2016). Likewise, compounds **318**, **319**, and **328–331** isolated from *Aquilaria sinensis* also had AChE inhibitory activity (Hashim et al. 2016; Yang et al. 2016a; Yang et al. 2016b). Zidorn observed that **125** isolated from *Lactuca tatarica* had free radical-scavenging activity and that its $IC_{50}$ was 5.52 μg/mL (Wang et al. 2010b). Compound **363** produced from *Daucus carota* had hepatoprotective activity (Fu et al. 2010a). In addition, compound **375** isolated from *Commiphora myrrha* had neuroprotective effects (Xu et al. 2012a). Moreover, compounds **287–288** isolated from *Daphne aurantiaca* had anti-insect activity (Huang et al. 2017).

## Conclusion

Sesquiterpenes are a focus of current research given their unique structural characteristics and various biological activities in natural products. This review summarized the extant literature on the distribution, chemical classification, and pharmacological effects of guaiane-type sesquiterpenes. Guaiane-type sesquiterpenes mainly exist in the form of inner esters, with the 12,6- guaianolide being the most common. They are distributed in approximately 70 genera of 30 families, and most belong to the Asteraceae, Lamiaceae, Thymelaeaceae, and Zingiberaceae families. These families have attracted considerable attention in the research field due to a large number of sesquiterpenes with major bioactive antitumor, antibacterial, and anti-inflammatory

**Table 3** NO inhibitory activities of guaiane-type sesquiterpenes from natural material

| Compounds | Plant origin | $IC_{50}$/μM | Ref. |
|---|---|---|---|
| **311** | *Curcuma wenyujin* | 22.36 ± 1.32 | (Xia et al. 2015) |
| **7** | *Artemisia austro-yunnanensis* | 4.20 ± 0.29 | (Chi et al. 2016) |
| **8** | | 10.67 ± 1.06, | |
| **9** | | 5.10 ± 0.58 | |
| **150** | *Chloranthus japonicus* | 13.33 ± 2.75 | (Zhuo et al. 2017) |
| **366** | *Daucus carota* | 46.9 ± 3.2 | (Fu et al. 2010a; Kim et al. 2007) |
| **367** | | 63.7 ± 1.3 | |
| **368** | | 29.6 ± 2.9 | |
| **164** | *Inula falconeri* | 0.29 | (Cheng et al. 2011) |
| **165** | | 0.13 | |
| **166** | | 9.64 | |
| **167** | | 3.94 | |
| **168** | | 41.2 | |
| **169** | | 19.53 | |
| **170** | | 0.11 | |
| **171** | | 7.3 | |
| **172** | | 5.94 | |
| **173** | | 12.86 | |
| **204** | | 0.07 | |
| **205** | | 2.18 | |
| **206** | | 0.40 | |
| **207** | | 8.34 | |
| **208** | | 20.3 | |
| **209** | | 10.8 | |
| **210** | | 0.36 | |
| **211** | | 2.05 | |
| **212** | | 9.89 | |
| **321** | *Pittosporum undulatum* | 8.1 | (Mendes et al. 2013) |
| **327** | | 7.2 | |
| **393** | | 73.1 | |
| **348** | | 16.4 | |
| **340** | *Salvia plebeia* | 30.68 | (Zou et al. 2018) |
| **134** | *Saussurea involucrata* | 98.01 ± 2.11 | (Xiao et al. 2011) |
| **256** | *Inula japonica* | 8.5 | (Zhu et al. 2013) |
| **257** | | 8.9 | |
| **258** | | 4.3 | |
| **259** | | 4.3 | |
| **260** | | 4.2 | |
| **261** | | 9.2 | |
| **269** | *Xylopia vielana* | 33.8 | (Xie et al. 2018b) |
| **275** | | 25.7 | (Xie et al. 2018a) |
| **277** | | 34.5 | (Xie et al. 2018c) |
| **281** | | 31.1 | |
| **301** | *Curcuma kwangsiensis* | 27.4 | (Xiang et al. 2018) |
| **302** | | 35.1 | |

effects. However, the bioactivity of these compounds is largely limited to in vitro studies. Guaianolides and guaiane polymers exerted various biological activities. Compounds with the 12,8-lactone ring structure (including 12,8-guaianolide, pseudoguaianolides and guaiane polymers which have anti-inflammation activities) have stronger biological activity than do those without this ring. Acetylation of hydroxyl groups tended to be more lipophilic, which leads to better penetration of cell membranes and enhanced inhibition of NO production, such as $IC_{50}$ of **204** reaching 0.07 μM for this reason. Compounds containing a peculiar structural trait of an oxygenated functionality exhibited more prominent effects, and their inhibitory effects were all less than 5 μM, just like **10**, **11**, and **13**. An extended discussion on the structure–activity relationship would require additional contributions to the literature.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.



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