JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Review

# The genus *Eremophila* (Scrophulariaceae): an ethnobotanical, biological and phytochemical review

Abdel Nasser Singab[a], Fadia S. Youssef[a], Mohamed L. Ashour[a,b] and Michael Wink[b]

[a]Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt and [b]Institute of Pharmacy and Molecular Biotechnology, Heidelberg University, Heidelberg, Germany

**Keywords**
*Eremophila*; ethnobotany; phytochemistry; Scrophulariaceae; secondary metabolites

**Correspondence**
Michael Wink, Institute für Pharmazie und Molekulare Biotechnologie, Universität Heidelberg, Im Neuenheimer Feld 364, 69120 Heidelberg, Germany.
E-mail: wink@uni-hd.de

Received February 10, 2013
Accepted May 9, 2013

doi: 10.1111/jphp.12092

## Abstract

**Objectives** *Eremophila* (Scrophulariaceae) is an endemic Australian genus with 214 species, which is commonly known as Fuchsia bush, Emu bush or Poverty bush. Plants of this genus played an important role for the Australian Aborigines who used them widely for medicinal and ceremonial purposes. Many studies have been carried out on many species of this genus and have generated immense data about the chemical composition and corresponding biological activity of extracts and isolated secondary metabolites.

**Key findings** Thorough phytochemical investigations of different *Eremophila* species have resulted in the isolation of more than 200 secondary metabolites of different classes with diterpenes as major constituents. Biological studies and traditional clinical practice demonstrated that *Eremophila* and its bioactive compounds possess various pharmacological properties. Plants were employed especially as a cardiotonic drug and also as potent anti-inflammatory, antimicrobial and antiviral agents.

**Summary** Further investigations are required to explore other *Eremophila* species, to evaluate the different biological activities of either their extracts or the isolated compounds and the possible underlying modes of action.

## Introduction

Throughout the ages, humans have traditionally relied on plants, animals and minerals for their basic needs, such as for food, protection against enemies, hunting, and healing of infections and health disorders. A number of traditional medicinal systems have evolved that have been used for centuries and today are still a source of interesting drugs for phytotherapy.[1]

Plants of the genus *Eremophila* represent perennial shrubs and small trees that occur endemically throughout the arid and semi-arid regions of Australia. The genus *Eremophila* has recently been included in the family Scrophulariaceae.[2] The name *Eremophila* is derived from the Greek words *Eremos* meaning 'desert' and *phileo* 'love', indicating that most of these species are adapted to live under the harsh conditions of the deserts and semi-arid places.[3] *Eremophila* comprises approximately 214 species, usually with alternate, shortly petiolate and lanceolate leaves with entire or dentate margin and acute apex. Many leaves are grey and hairy, and are thus protected against intensive light. The axillary single flowers have a conspicuous yellow to greenish or red corolla.[4,5] More than 70% of the plants are pollinated by insects (entomophily), the others are visited by birds (ornithophily). Fruits are fleshy or dry capsules containing one to twelve seeds. Plants are commonly known as Fuchsia bush or Emu bush and many species have been used traditionally for treatment of many ailments or for ceremonial purposes for aboriginal people.[6] Some species are toxic to stock (Poison bush), others are weedy and populate degraded or overgrazed land (Poverty bush).

The family Scrophulariaceae is a large family with almost 87 genera and 4800 species.[4] Plants of this family are widely used in traditional medicine and phytotherapy.[1] The corresponding biological activities are related to the richness of secondary metabolites such as phenylpropanoids, iridoid glucosides, and terpenoids with anti-inflammatory, antinociceptive, wound healing and antimicrobial activities.[7,8] In addition, many species are rich with polyphenols, flavolignans and phenolic acids,

which exhibit antiprotozoal, antioxidant, antibacterial and cytotoxic properties.[9–13]

Phytochemical investigations of the genus *Eremophila* have led to the isolation and identification of more than 200 secondary metabolites from several classes.[14] Major secondary metabolites include diterpenes (eremane, cembrene, decipiane, and viscidane type); others are triterpenoids, verbascosides, cyanogenic glucosides, fatty acids, phenylpropanoids, lignans and flavonoids.[6]

Many researchers have explored the biological and pharmacological properties of several *Eremophila* species, such as antimicrobial, antiviral, antiproliferative, anti-inflammatory and immunomodulatory activities.[12,15–18] Due to the biological and ethnopharmacological importance of *Eremophila*, much work has been carried out on the genus *Eremophila* since the early published review written by Ghisalberti[6] in 1994. Since that time, an immense amount of data has been generated regarding the chemistry and biology of many other species within this genus. In an effort to better understand and present an overview of the *Eremophila* order, the data on the recently isolated compounds as well as the biological activity of different members of this medicinally important genus has been compiled and summarised. Relevant data up until December 2012 has been collected from different databases including Scifinder (https://scifinder.cas.org/scifinder/login) for phytochemistry related research, PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), and Web of Knowledge (http://www.webofknowledge.com) for ethnobotanical and biological related research. We aim to derive an impressive and convenient review; scientifically beneficial for both investigators and readers who are interested in the pharmaceutical aspects of medicinally active herbs, since no other compilation of literature was found regarding this genus. However, it was not the intention of this review to go beyond the field of phytochemistry and ethnobotany.

## Ethnobotany

*Eremophila* species have been used by Australian Aboriginal people for cultural, religious and material purposes. Historically, these plants were employed for cleansing and strengthening a new-born child, in ceremonies to appease totemic ancestors, in initiation rites, and in the lining of graves and shrouding the bodies of the dead. Additionally, the plant resins, obtained from their leaves and branchlets, were used as varnish or as a natural cement or sealant.[6,19]

Approximately 70 plant species were used medicinally by the native Australians for the alleviation of the symptoms of many respiratory tract infections, such as common cold, cough, chest pain, and fever. They were also taken for the treatment of several gastrointestinal disorders, diarrhoea, rheumatic pain, and headache. Topically, most of *Eremophila* preparations were employed to treat minor wounds, dermatological lesions and infections, body sores and scabies.[20–24]

The commonly used *Eremophila* species, their parts used, methods of administration, and traditional uses are summarized in Table 1. Although it is not our intention to elaborate the ethnobotanical utilizations of all *Eremophila* species, a few of them will be mentioned:

*E. alternifolia* has long been regarded as the 'number one medicine' by the native Australians.[21] Infusions made from the leaves are used internally and externally as decongestant, expectorant and analgesic. These treatments are said to alleviate colds, influenza, fever and headaches and were used to medicate septic wounds, to induce sleep and to promote general well- being (Table 1).[4,21,22,24–28]

Ethnobotanical reports provide information on the traditional medicinal use of *E. duttonii* against several microbial infections. These include topical preparations for the treatment of minor dermal wounds, infected lesions derived from infestation by the scabies mites (*Sarcoptes scabiei*), and of ophthalmic and oto-nasopharyngeal complaints. Extracts from this species are reputed to have insect repelling properties.[21]

*E. longifolia* has been used traditionally against a wide range of health disorders and aqueous decoctions of the leaves represent one of the most popular and widespread therapeutic remedies in routine use by contemporary indigenous Australian people.[24] They include treatment of the symptoms of respiratory tract infections, gastrointestinal distress and headache, along with topical applications of minor wounds, dermatological lesions, ophthalmic complaints and dermal parasitism by scabies mites.[20–24] The decoctions of the leaves were prepared for eye washes, as counter-irritants, and for skin and body washes.[25,27] In addition, the use of liniments, composed mainly of the crushed leaves, for joint and skeleto muscular pain has also been reported.[21–23] The inhalation of steam from heated leaves is said to be beneficial against respiratory infections and general illness.[22]

*E. maculata* was not often used by native Australians because it was not abundant. It was employed as a blister for the treatment of colds (Table 1). However, this species was also classified as stock poison as early as 1887 and in 1910 due to the presence of the cyanogenic glucoside prunasin, which releases the very toxic hydrogen cyanate upon enzymic hydrolysis.[14]

## Biological activity

### Cardioactive properties

The cardiotonic activity of several *Eremophila* species has been studied previously (Table 2).[29–40] The crude aqueous and methanol extracts of *E. alternifolia* leaves and bark

**Table 1** Some traditional uses for common *Eremophila* species

| Plant species | Part used | Traditional uses | References |
|---|---|---|---|
| *E. alternifolia* | Leaves | As decongestant, expectorant and analgesic<br>Alleviation of cold, influenza, fever and headaches<br>As antiseptic for wounds<br>As sleeping aid and for general well-being | [14,21,22] |
| *E. cuneifolia* | Leaves | Relieving common cold and headache | [14] |
| *E. dalyana* | Leaves | Treatment of colds and other chest ailments<br>As a body wash for scabies | [6] |
| *E. duttonii* | Leaves | Treatment of minor dermal wounds and infected lesions derived from infestation by the scabies mites<br>Treatments of ophthalmic and oto-nasopharyngeal complaints<br>Insect repelling properties | [21] |
| *E. fraseri* | Leaves | To alleviate colds and<br>To cure toothache and rheumatism<br>As a sealant and an adhesive | [19] |
| *E. freelingii* | Stems and leaves | Against cough, common cold, and fever<br>Against chest and body pain<br>To alleviate diarrhoea | [25,26] |
| *E. gilesii* | Leaves | Treatment of colds, headache, chest pain<br>As antibacterial agent for sores | [3] |
| *E. latrobei* | Stems and leaves<br>Leaves | For treatment of malaise, colds, influenza cough, respiratory tract infections<br>As antibacterial agent for sore throat<br>For treatment of scabies<br>For the smoke treatment of sick people | [23,25,27]<br>[6] |
| *E. longifolia* | Leaves | Treatment of respiratory tract infections and headache<br>Antiseptic for minor wounds, dermatological lesions, ophthalmic complaints and dermal infestation by the scabies mite<br>Relieve joint and skeleto- muscular pain, general illness | [20–24]<br>[21–23] |
| *E. maculata* | Leaves | For treatment of common cold<br>It was classified as a stock poison | [14] |
| *E. mitchellii* | Wood | In perfume industry | [28] |
| *E. sturtii* | Leaves<br>Branches | As a treatment for cough, and respiratory infection<br>As a wash for sores and cuts<br>Have fly repellent properties | [25]<br>[26] |
| *E. paisley* | Twigs and leaves | As a body wash in the treatment of scabies | [6] |

mediates an initial, but transient, positive inotropic effect. A decrease occurred simultaneously with increased coronary perfusion rate. The induced effects lasted less than 15 min followed by full recovery to the normal levels.

The phenylpropanoid verbascoside (**197**), isolated from the methanol and water extracts of *E. alternifolia* leaves, mediated a significant positive chronotropism, inotropism and coronary perfusion rate (CPR) in the rat heart.[41] The iridoid glucoside geniposidic acid, isolated from the methanol extract of *E. longifolia* leaves, had an opposite effect with a significant negative chronotropism, inotropism and CPR. Both verbascoside and geniposidic acid (**10**) caused significant, but opposite, changes in rat heart activity.[32] The verbascoside effects were similar to those reported by Pennacchio *et al*.[31] for the methanol and aqueous extracts of *E. alternifolia* leaves. That finding suggested that verbascoside was responsible for the cardiotonic activity reported for the original extracts.[31] The sugar alcohol mannitol (**200**) may also have played a small role in the CPR response mediated by these extracts. In a preliminary study, the increase in CPR was enhanced when verbascoside and mannitol were co-administered.[32] Similar mannitol-induced increases in CPR have been reported by others. Willerson *et al*.[42] and Fixler *et al*.[43] showed that mannitol improved coronary blood flow in ischaemic myocardium of experimental animals, while geniposidic acid significantly decreased heart rate, contractile force and CPR.[32] A recent study suggested that verbascoside increases heart rate, contractile force and coronary perfusion rate via a cAMP-dependent mechanism. Injection of verbascoside (1 mM) significantly increased intracellular levels of cAMP up to 1733%, which in turn increased the levels of prostacyclin.[41]

A methanol extract from *E. alternifolia* induced significant changes to the heart activity of spontaneous hypertensive rats. Four concentrations of extract were prepared: 16, 32, 64 and 128 mg/ml. The 128 mg/ml dose of the

**Table 2** Summary of the most relevant biological activity of different *Eremophila* species

| Plant species | Extract/substances | Main pharmacological activity | References |
|---|---|---|---|
| *E. alternifolia* | Ethanol extract | Inhibition of antigen production in human cytomegalovirus (HCMV) | [16] |
| | Methanol and water extracts (verbascoside) | Antibacterial activity | [29] |
| | | Anti-listerial activity | [30] |
| | | Increases chronotropism, inotropism, and coronary perfusion rate (CPR) | [31–33] |
| | | Antimycobacterial activity | [34] |
| *E. duttonii* | Ethanol extract | Antibacterial activity against Gram-positive bacteria | [29] |
| | (a) serrulat-14-en-7,8,20-triol | Anti-listerial activity | [30,35] |
| | (b) serrulat-14-en-3,7,8,20-tetraol | Antibacterial activity against Gram-positive bacteria | [6] |
| | (c) 4-hydroxy-4-methyl-1-(2,3,4,5-tetrahydro-5-methyl[2,3′-bifuran]-5-yl)pentan-2-one | | |
| *E. freelingii* | Methanol extract | Inhibition of platelet aggregation and 5-HT release | [18] |
| | | Antibacterial activity | [36] |
| *E. latrobei* subsp. *glabra* | Ethanol extract | Inhibit the development of Ross River virus (RRV)-induced cytopathic effect (CPE) | [16] |
| | | Antibacterial activity | [36] |
| *E. longifolia* | Ethanol extract | Inhibition of antigen production in HCMV | [16] |
| | Methanol extract | Antimycobacterial activity | [34] |
| | Methanol extract (geniposidic acid) | Anticariogenic characteristics | [37] |
| | | Antibacterial activity | [36] |
| | | Inhibitory effect with negative chronotropism, inotropism, and CPR | [32] |
| | | Inhibition of platelet aggregation and 5-HT release | [18] |
| *E. maculata* | Water-ethanol extract | Xanthine oxidase inhibitor | [38] |
| | | Antibacterial activity | [33] |
| *E. mitchellii* | Wood, leaf, branch and root oil (eremophilone) | Cytotoxic effect on P388D1 mouse lymphoblast cells | [17] |
| *E. neglecta* | Ether extract | Antimicrobial activity against *Staphylococcus aureus* | [39] |
| | (a) 8,19-dihydroxyserrulat-14-ene | Antimicrobial activity against Gram-positive bacteria *S. aureus, Streptococcus pyogenes*, and *S Streptococcus pneumoniae*. | |
| | (b) 8-hydroxyserrulat-14-en-19-oic acid | | |
| | (c) Biflorin | | |
| *E. serrulata* | Ether extract | Antimicrobial activity against *S. aureus* | [40] |
| | (a) 9-methyl-3-(4-methyl-3-pentenyl)-2,3-dihydronaphtho[1,8-bc]pyran-7,8-dione | | |
| | (b) 20-acetoxy-8-hydroxyserrulat-14-en-19-oic acid. | | |
| | (c) 8,20-dihydroxyserrulat-14-en-19-oic acid | | |
| | (d) 8,20diacetoxyserrulat-14-en-19-oic acid | | |
| *E. sturtii* | Ethanol crude extract | Inhibition of cyclooxygenase (COX)-1 and COX-2 | [12] |
| | 3,8-dihydroxyserrulatic acid | Antibacterial activity | |
| | Serrulatic acid | Weak inhibition of COX-1 and COX-2 | |
| | | Potent bactericidal activity against *S. aureus* | |
| | | Strong inhibition of COX-1 and COX-2 | |
| | | Potent bactericidal activity against *S. aureus* | |

*E. alternifolia* leaf extract significantly reduced the systolic blood pressure of hypertensive rats, but this was only a 0.5% decrease and the dose was very high. Diastolic blood pressure was not affected by any of the concentrations. The heart rate was increased dose-dependently after administration of 16, 32 or 64 mg/ml by 10.4, 11.2 and 7.4%, respectively. There was no significant change following the introduction of the highest dose.[33]

## Anti-inflammatory and immunomodulatory activities

The total crude ethanol extract of *E. sturtii* along with several fractions and isolated compounds were examined as inhibitors of both cyclooxygenase (COX-1, COX-2) and 5-lipoxygenase to assess a potential anti-inflammatory activity. At a dose of 2 mg/ml the ethanol extract inhibited COX-1 and COX-2 by 95 and 89%, respectively. Among the tested fractions, the ethyl acetate partition was the most active, resulting in a 88 and 66% inhibition of COX-1 and COX-2 at the same dose. The two isolated diterpenes of the serrulatane type 3,8-dihydroxy serrulatic acid (**114**) and serrulatic acid (**118**) exhibited different activity profiles. The first compound had weak COX-1 and COX-2 inhibitory activity, while the second compound strongly inhibited both enzymes with IC50 values of 27 and 73 μg/ml for COX-1 and COX-2, respectively. No inhibition of 5-lipoxygenase by either compound was observed.[12]

Xanthine oxidase is the enzyme responsible for the formation of uric acid from the purines hypoxanthine and xanthine, and is responsible for the medical condition known as gout. Xanthine oxidase also serves as an important source of reactive oxygen species (ROS) that contribute to oxidative damage of living tissues; ROS are involved in many pathological processes such as inflammation and cardiovascular disorder.[44] At a dose of 50 μg/ml *E. maculata* extract inhibited xanthine oxidase by 61%.[38]

Methanolic extracts of *E. freelingii*, and *E. longifolia* were potent inhibitors of ADP-induced 5-HT release from human platelets *in vitro* (62.13 and 65.70% inhibition, respectively, at a dose of 50 mg/ml). The activity was retained in the dichloromethane fraction of *E. freelingii*, suggesting that there could be two different types of compounds causing the inhibition of platelet function.[18]

## Antimicrobial activity

The antimicrobial activity of *Eremophila* extracts as well as of corresponding isolated compounds has been extensively studied (Table 2).[15] Promising activity against Gram-positive bacteria was obtained.

Ethanol extracts of various parts of 39 plants used in traditional Australian aboriginal medicine have been screened for antimicrobial activity. Extracts from *Eremophila* leaves were most potent, with *E. duttonii* exhibiting the highest activity against Gram-positive bacteria, such as *Bacillus cereus*, *Enterococcus faecalis*, *Staphylococcus aureus* and *Streptococcus pyogenes*, in agar diffusion assays; diameters of inhibition zones were 10, 9, 12, 14 mm, respectively, at a concentration of 77 μg/ml extract.[36] Ethanol extracts of *E. alternifolia* and *E. duttonii* inhibited clinical isolates of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[29]

The active species *E. duttonii* was further evaluated against other Gram-positive bacteria such as *Clostridium* spp. (*C. perfringens*, *C. sporogenes*) and *Listeria monocytogenes*. The plant extract showed promising antibacterial properties against these food-borne pathogens. A preliminary phytochemical investigation using TLC bioautography suggested that the antibacterial activity may be attributed to the presence of sterols and other terpenoids.[35] A thorough phytochemical investigation of the hexane fraction of *E. duttonii* led to the isolation and identification of two terpenoids, 7,8,20-trihydroxyserrulat-14-ene (**108**) and serrulat-14-en-3,7,8,20-tetraol (**117**): they are regarded as the principal constituents responsible for antibacterial activity against *S. aureus*, *Staphylococcus epidermidis* and *Streptococcus pneumoniae*.[45] A recent study carried out by Ndi *et al*.[46] showed that these two polar diterpenes are highly unstable when separated due to the oxidation of their phenolic hydroxyl groups into quinones, which are essential for the antibacterial activity of this class of compounds.

Bioassay-guided fractionation of the diethyl ether extract of *E. neglecta* led to the isolation of three new serrulatane-type diterpenoids. Two of these compounds showed antimicrobial activity against Gram-positive bacteria including *S. aureus, S. pyogenes*, and *S. pneumoniae*.[39] The bioactivity spectrum of these compounds was recently examined across a wider range of Gram-positive and Gram-negative bacteria including human and veterinary pathogens, and some multidrug-resistant isolates to explore the range of potential utility of these novel antibacterials. Both 8,19-dihydroxyserrulat-14-ene (**103**) and 8-hydroxyserrulat-14-en-19-oic acid (**105**) exhibited antibacterial activity against all Gram-positive bacteria tested. The only activity for the two compounds against five Gram-negative bacteria tested was observed against *Moraxella catarrhalis*, which can cause chronic obstructive pulmonary disease, with minimum inhibitory concentrations (MIC) of 3.1 and 6.2 μg/ml for the two compounds, respectively.[47]

In the same context, *o*-naphthoquinone (**126**) and 20-acetoxy-8-hydroxyserrulat-14-en-19-oic acid (**115**), isolated from the leaves of *E. serrulata*, showed antimicrobial activity against *S. aureus*. The *o*-naphthoquinone was the most active with an MIC of 15.6 μg/ml and a minimum bactericidal concentration (MBC) of 125 μg/ml. This compound showed antimicrobial activity against other Gram-positive bacteria including *S. pyogenes* and *S. pneumoniae*.[40] The ethanol extract of *E. sturtii* leaves as well as its ethyl acetate fraction exhibited antibacterial activity against *S. aureus*. Two novel serrulatane diterpenes were isolated, 3,8-dihydroxyserrulatic acid (**114**) and serrulatic acid (**118**), with the latter exhibiting the most potent bactericidal activity against *S. aureus*.[12]

The antibacterial activity could be attributed to amphiphilic phytosterols and terpenoids that function as

detergents. The terpenoids interact with biomembranes: while their lipophilic moiety intercalates with phospholipids and other lipids, hydrophilic moieties remain outside the cell and can interact with glycoproteins or glycolipids. As a result there is a loss of membrane integrity and fluidity occurs, with the subsequent leakage of many polar molecules out of the cells or the entry of unwanted molecules into a cell.[48]

Ndi *et al*.[49] examined the antimicrobial activity of 72 *Eremophila* extracts against 68 clinical isolates of multi-resistant methicillin-resistant *S. aureus* (MRSA). An extract of *E. virens* inhibited growth of all the tested clinical isolates at the minimal test concentration of 31 μg/ml. This study has highlighted that a number of different *Eremophila* species possess relevant antibacterial activity against Gram-positive human pathogens.

The ethanol extract of *E. longifolia* stems inhibits *Streptococcus mutans* and *Streptococcus sobrinus*. Preliminary phytochemical analysis of the active fractions established that the active compounds were phenolics.[37] Moreover, the ethanol extract of *E. maculata* leaves showed potent antimicrobial activity against three Gram-positive bacteria.[33] Presence of reactive phenolic OH groups is one of the main reasons for the potent antibacterial activity. The phenolic hydroxyl groups can partly dissociate under physiological conditions resulting in $O^-$ ions. The charged and polar polyphenols interact with proteins by forming hydrogen and ionic bonds with several bacterial and fungal peptides and proteins, which might lead to protein inactivation and loss of function.[50,51]

In a recent study to assess the anti-listerial activity of *E. alternifolia* and *E. duttonii* extracts, a growth inhibition of *Listeria monocytogenes* was recorded in agar-diffusion assays with inhibition zones of 8.8 and 9.6 mm, respectively.[30]

Although most of the work has been conducted against Gram-positive microbes, the extracts of *E. alternifolia* and *E. longifolia* showed a very promising activity against *Mycobacterium fortuitum* and *Mycobacterium smegmatis* using a plate diffusion assay.[34]

### Antiviral activity

The antiviral activity of *Eremophila* has not been fully investigated. Albeit of many reports on their antimicrobial activity as mentioned in the previous section, only one report was found concerning antiviral properties. Semple *et al*.[16] evaluated the activity of extracts against one DNA virus (human cytomegalovirus, HCMV) and two RNA viruses (Ross River virus (RRV) and poliovirus type 1). The ethanol extract of *Eremophila latrobei* subsp. *glabra* inhibited the cytopathic effect of RRV by more than 25% (effective concentration 25–102 μg/ml). A weak inhibition of HCMV late antigen production was exhibited by the extracts of *E. alternifolia* and *E. longifolia*.

### Cytotoxicity

Cytotoxic activity of different *Eremophila* extracts and isolated compounds has hardly been explored (Table 2). The activity of wood oil and isolated pure compounds of *E. mitchellii* were evaluated against P388D1 mouse lymphoblast cells. All of the tested samples exhibited a potent antiproliferative activity. The IC50 values ranged between 51–110 μg/ml, whilst the pure compounds eremophilone (**42**), 9-hydroxy-7(11),9-eremophiladien-8-one (**45**), 8-hydroxy-1,11-eremophiladien-9-one (**50**), and santalcamphor (**52**) exhibited IC50 values between 42 and 105 μg/ml. Eremophilone was the most active isolate in this study, and was comparable with the curcumin control (IC50 = 19 μg/ml). It should be noted that the leaf oil which is chemically distinct from the wood or root oils, also exhibited significant cytotoxic effects.[17]

In a recent study, Anakok *et al*.[47] evaluated the antibacterial and antiproliferative activity of 8,19-dihydroxyserrulat-14-ene (**103**) and 8-hydroxyserrulat-14-en-19-oic acid (**105**), two serrulatanes isolated from *E. neglecta*. Both compounds showed a very promising activity against Vero cells with IC50values of 9.2 and 20.0 μg/ml.

## Phytochemistry

### Monoterpenes and iridoids

Monoterpenes are not widely represented in the genus *Eremophila*; only a restricted number of *Eremophiia* species has been analysed by GLC-MS.[21] A few monoterpenes have been identified: geranyl acetate (**1**) is the major component in *E. abietin*, 1,8-cineole (**2**) in *E. scoparia* and *E. dalyana*, (+)-verbenone (**3**) in *E. dempsteri*, and (+)-fenchone (**4**) in *E. caerulea*.[14,52–54] *E. alternifolia* yielded 4% essential oil mainly composed of fenchone (**4**) and limonene (**8**). α-Pinene (**9**) predominated the essential oils from *E. duttoni*, *E. freelingii* and *E. longifolia*, which were produced in small amounts (<1%).[14]

The volatile oil of *E. longifolia* leaves showed a total of 33 compounds which were identified by GLC/MS. Isomenthone (**13**) and menthone (**14**) were the major monoterpenes. Other constituents found in high quantities included α-terpineol (**15**) and piperitone (**16**). The essential oil also contained a number of monoterpene hydrocarbons including limonene (**8**), 4-carene (**17**) and α-terpinene (**18**), along with the monoterpene alcohols linalool (**19**) and menth-2-en-1-ol (**20**). The oil exhibited a pleasant ethereal peppermint-like smell, most likely due to the presence of isomenthone (**13**) and menthone (**14**), along with other *p*-menthane terpenoids (**12**).[55]

Iridoid glucosides (a monoterpene from a biosynthetic point of view), which are typical secondary metabolites of Scrophulariaceae, have been recorded for a few *Eremophila* species. Geniposidic acid (**10**) has been isolated by methanol extraction of a sample from *E. cuneifolia* after ether and acetone extraction.[14] The iridoid glucoside catalpol (**11**) was isolated from the aqueous extract of the fruits of *E. maculata* var. *brevifolia* (Table 3).[56,57]

## Sesquiterpenes

### Furanosesquiterpenes

Furanosesquiterpenes represent a group of sesquiterpenes which are essentially oxygenated farnesols and characteristic for the essential oil of some *Eremophila* species. The best known of these is (-)-ngaione (**21**) isolated from *E. latrobei*, (-)-10,11-dehydrongaione (**22**) and (-)-10,11-dehydroepingaione (**23**) from *E. rotundifolia*, (±)-myoporone from *E. maculata, E. latrobei* and *E. miniata*, (+)-myoporone (**25**) from *E. inflata*, and (-)-10,11-dehydromyoporone (**26**) from *E. maculata*.[14,58–61]

Freelingyne (**27**), an acetylenic furanosesquiterpene was isolated for the first time from natural sources (**3**) in *E. freelingii* with its 8,9-dihydro- (**28**) and 4,5,8,8,9,9-hexahydro-analogues.[62–64] However, later freelingyne was detected in *E. rotundifolia*.[65] In addition, freelingnite (**29**) was the first example of a 4-alkylbut-2-enolide isolated from higher plants in *E. freelingii*.[64]

Eremoacetal (**30**), an unique furanosesquiterpene containing a 2,8-dioxabicyclo [3.2.1] octane skeleton, is a component of the extracts from *E. rotundifolia*.[59] This species also produces a series of other furanosesquiterpenes including dendrolasin (**31**), 4-hydroxydendrolasin (**32**), and the isomeric dihydrophymaspermones (**33**) (Table 4).[59,66–68]

### Cyclic sesquiterpenes

Members of the genus *Eremophila* produce a number of cyclic sesquiterpenes belonging to the structural bisabolene, eudesmane, eremophilane, aromadendrane, cadinane and zizaene types.[14]

The presence of unusual terpenoid metabolites with a ketone group became evident as early as 1932 with the isolation of eremophilone ketone and its oxygenated derivatives from the wood oil of *E. mitchellii*.[17,28,69] Subsequently, it was suggested that the skeleton, of what now has become known as the eremophilane type, arises by methyl migration in precursors possessing the isoprenoid skeleton and configuration of the normal and biosynthetically regular eudesmanes.[14]

The presence of eudesmol has been established and three derivatives accumulate in *E. scoparia*.[70] Also, β-eudesmol (**56**) was found to be present in *E. drummondii* var. *brevis, E. cuneifolia*, *E. dalyana*, *E. flaccida*, *E. leucophylla* and *E. subfloccosa*.[14,53,71,72] Nevertheless, eremophilanes, e.g. eremophilone (**42**) and eudesmane sesquiterpenes are dominant in only three species: *E. mitchellii*, *E. scoparia* and *E. rotundifolia*.[17,28,65,69,70] Two aromatic sesquiterpenes, (1*R*, 4*R*)-calamenene (**60**) and (1*R*, 4*R*)-7-hydroxy-calamenene (**61**) characterize the essential oils of *E. drummondii* and *E. virens*.[73,74] The unusual keto alcohol (+)-oplopanone (**62**) was isolated from *E. miniata*.[61]

The chemical analysis of the resins from leaves and terminal branches of *E. virgata* and *E. interstans* revealed a complex mixture of oxygenated sesquiterpenes.[75,76] Separation of these secondary metabolites led to the identification of five new cadinene sesquiterpenes (**65–69**). Another group of sesquiterpenes represented in *Eremophila* belong to the zizaene series with the tricyclo[6.2.1.0.$^{1,5}$]undecane skeleton. The four ent-zizaene compounds (**70–73**) have been detected in *E. georgei*, *E. metallicorum* and *E. subteretifolia* (Table 5).[14,77–80]

### Diterpenes

*Eremophila* species are a major source for novel diterpenes. A focus has been on desert adapted species, many of which carry resin coating on the leaves and terminal branches which can amount to up to 20% of the dry weight. These viscous films are thought to provide a means against evaporation on one hand, and chemical defence against herbivores and microbes on the other hand. This resin can easily be removed with ether or acetone and, with few exceptions, is composed of a mixture of oxygenated diterpenes. The first indication of the presence of unusual diterpenes in *Eremophila* came with the isolation of eremolactone from *E. fraseri* and *E. freelingii* in 1962.[81,82] However, since this time several diterpenes have been isolated and identified. These diterpenes can be categorized as shown in the following (Table 6).[83–104]

### Acyclic and monocyclic diterpenes

The best examples of these diterpenes are the acyclic metabolites (**74–84**) isolated from *E. exilifolia*, *E. glutinosa* and *E. petrophila*.[14,83,84] These compounds can be regarded as oxygenated derivatives of the C20 alcohol geranylgeraniol.

### Cembrenes

Cembrenes are macrocyclic diterpenes containing a 14-membered ring. The first example of a cembrene from *Eremophila* was epoxycembranediol (**85**) isolated from the resin of *E. georgei*.[85] Subsequently, *E. abietina*, *E. clarkei, E. dempsteri*, *E. granitica*, *E. fraseri*, *E. platycalyx* and *E. metallicorum* have all been shown to produce several

**Table 3** Structures and distribution of secondary metabolites of *Eremophila*: chemical structures of the isolated monoterpenes

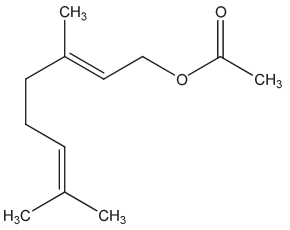
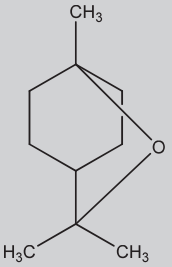
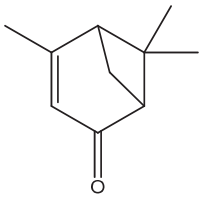
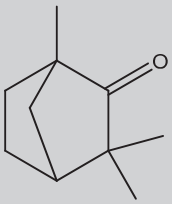
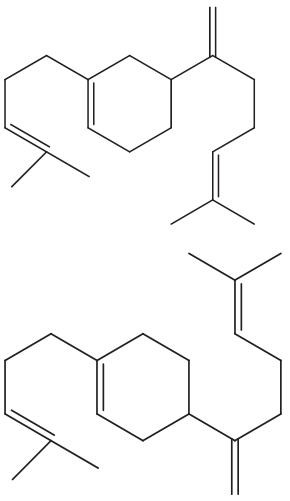
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| Geranyl acetate (**1**) |  | *E. abietina* | [52] |
| 1,8-Cineole (**2**) |  | *E. scoparia*<br>*E. dalyana* | [14]<br>[53] |
| (+)-Verbenone (**3**) |  | *E. dempsteri* | [54] |
| (+)-Fenchone (**4**) |  | *E. caerulea*<br>*E. alternifolia* | [14]<br>[14] |
| *m*- and *p*-Camphorene (**5** and **6**, respectively) |  | *E. cuneifolia* | [6,57] |

**Table 3** Continued.

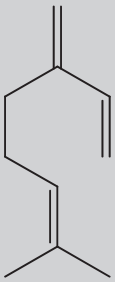
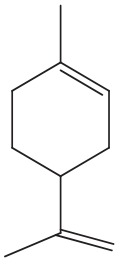
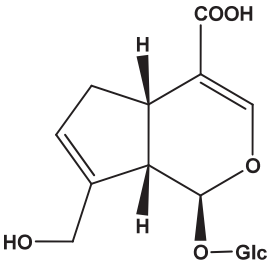
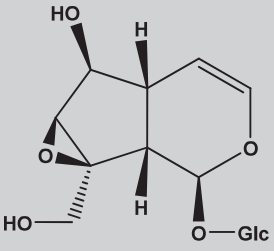
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| Myrcene (**7**) |  | *E. cuneifolia* | [14] |
| Limonene (**8**) |  | *E. alternifolia*<br>*E. longifolia* | [14]<br>[55] |
| α-Pinene(**9**) |  | *E. duttoni*<br>*E. freelingii*<br>*E. longifolia* | [14] |
| Geniposidic acid (**10**) |  | *E. cuneifolia*<br>*E. longifolia* | [14]<br>[32] |
| Catalpol (**11**) |  | *E. maculata* | [56] |

**Table 3** Continued.

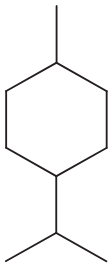
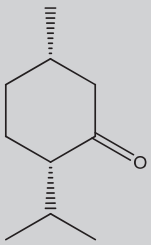
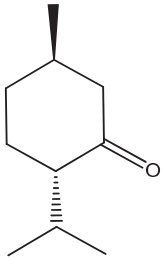
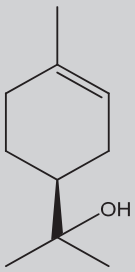
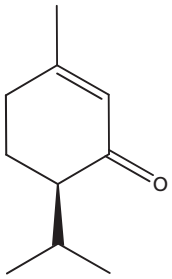
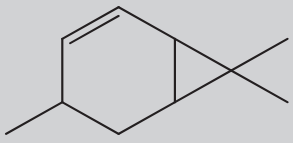
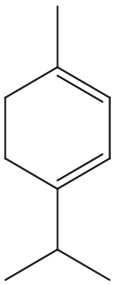
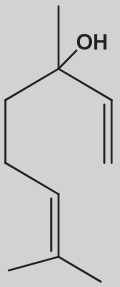
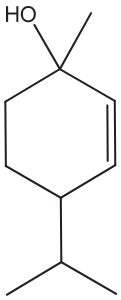
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| *p*-Menthane (**12**) |  | *E. longifolia* | [55] |
| Isomenthone (**13**) |  | *E. longifolia* | [55] |
| Menthone (**14**) |  | *E. longifolia* | [55] |
| α-Terpineol (**15**) |  | *E. longifolia* | [55] |
| Piperitone (**16**) |  | *E. longifolia* | [55] |
| 4-Carene (**17**) |  | *E. longifolia* | [55] |

**Table 3** Continued.

| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| α-Terpinene (**18**) |  | *E. longifolia* | [55] |
| Linalool (**19**) |   | *E. longifolia* | [55] |
| Menth-2-en-1-ol (**20**) |   | *E. longifolia* | [55] |

biologically active cembrene metabolites.[14,52,54,86] These carry the same absolute configuration at C-1 and all retain the double bond at C-12 with differences in the levels of oxidation on methyl groups at C4 and C8. The observation that both the acyclic and cembrene diterpenes from *Eremophila* contain *cis* double bonds indicate that they derive from a common biosynthetic intermediate.

## Polycyclic diterpenes

These diterpenes arise from a sesquiterpene-type cyclization process involving only the first three isoprene moieties in a C20 (geranylgeranyl pyrophosphate) precursor. As a consequence, the skeletons generated can be considered as isoprene analogues of sesquiterpenes. The first three bisabolene isoprenologues (**96**–**98**) of this type, which were isolated from *E. foliosissima*, contained a single carbocyclic system.[87,88]

## Serrulatanes

Bicarbocyclic serrulatanes represent the most common diterpene skeleton in *Eremophila*. The first example of this type was dihydroxyserrulatic acid (**101**) isolated from *E. serrulata*.[89,90] Most of the serrulatanes differ simply in the degree and position of oxygenation around the skeleton. Structural variants have been detected in *E. biserrata*, *E. decipiens*, *E. denticulata*, *E. drummondii*, *E. drummondii*, *E. falcata* and many others.[74,89,90,92] *E. latrobei* produces biflorin (**128**) as the major diterpene.[74] These serrulatane diterpenes are regarded as isoprenologues of the calamenene type.

**Table 4** Structures and distribution of secondary metabolites of *Eremophila*: chemical structures of the isolated furanosesquiterpenes

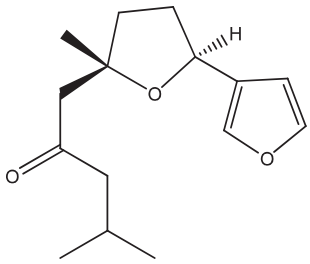
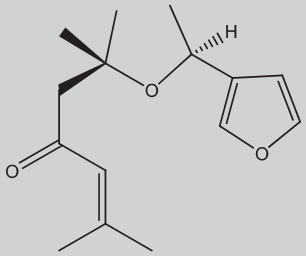
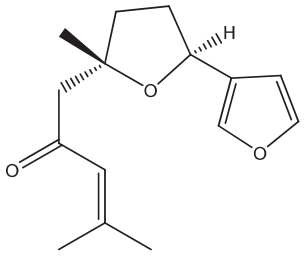
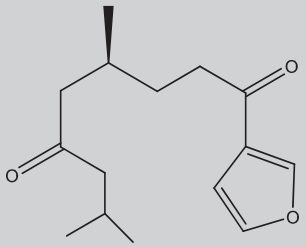
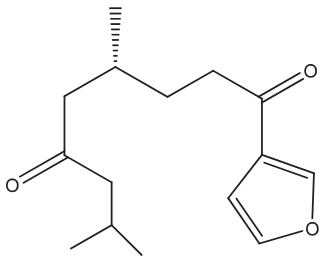
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| (-)-Ngaione (**21**) |  | *E. latrobei* | [58] |
| (-)-10,11-Dehydrongaione (**22**) |  | *E. rotundifolia* | [59] |
| (-)-10,11-Dehydroepingaione (**23**) |  | *E. rotundifolia* | [59] |
| (+/-)-Myoporone (**24**) |  | *E. maculata*<br>*E. latrobei*<br>*E. miniata* | [60]<br>[60]<br>[61] |
| (+)-Myoporone (**25**) |  | *E. inflata* | [14] |

**Table 4** Continued.

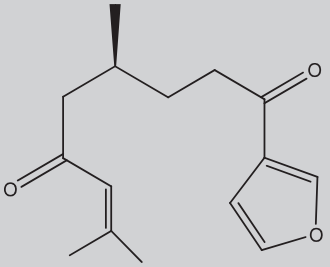
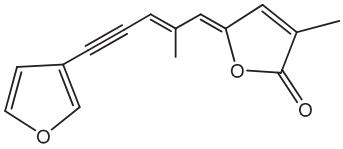
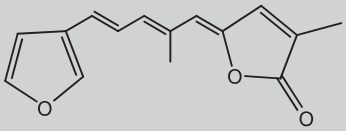
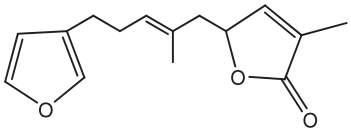
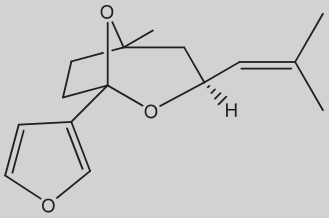
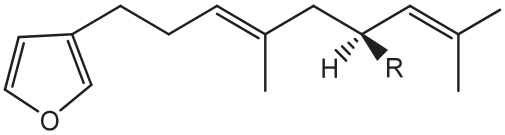
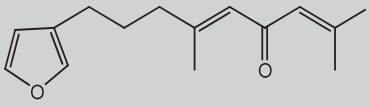
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| (-)-10,11-Dehydromyoporone (**26**) |  | *E. maculata* | [60] |
| Freelingyne (**27**) |  | *E. freelingii*<br>*E. rotundifolia* | [62,63]<br>[65] |
| 8,9-Dihydro-freelingyne (**28**) |  | *E. freelingii* | [63] |
| Freelingnite (**29**) |  | *E. freelingii* | [64] |
| Eremoacetal (**30**) |  | *E. rotundifolia* | [59] |
| |  | | |
| Dendrolasin (**31**) | R = H | *E. rotundifolia* | [66] |
| 4-Hydroxydendrolasin (**32**) | R = OH | *E. rotundifolia* | [66] |
| Dihydrophymaspermones (E- and Z-) (**33**) |  | *E. rotundifolia* | [59] |

**Table 4** Continued.

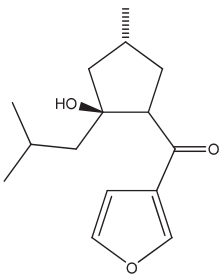
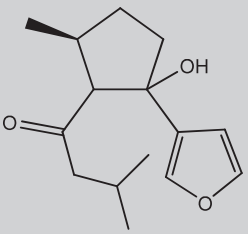
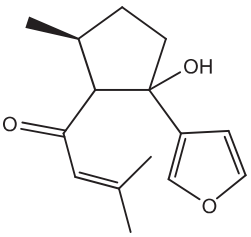
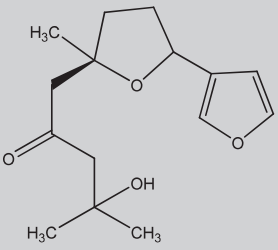
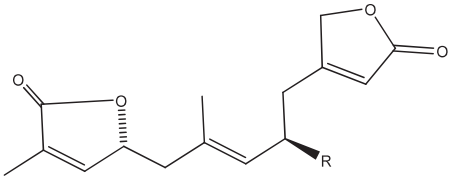
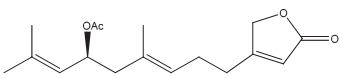
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| 9-Hydroxy-5,9-dihydromyomontanone (**34**) |  | *E. alternifolia*<br>*E. latrobei*<br>*E. scoparia* | [67] |
| 4-Hydroxydihydromyodesmone (**35**) |  | *E. alternifolia*<br>*E. latrobei*<br>*E. scoparia* | [67] |
| 1-((5*S*)-2-(Furan-3-yl)-2-hydroxy-5-methylcyclopentyl)-3-methylbut-2-en-1-one (**36**) |  | *E. alternifolia*<br>*E. latrobei*<br>*E. scoparia* | [67] |
| 4-Hydroxy-4-methyl-1-(2,3,4,5-tetrahydro-5-methyl[2,3′-bifuran]-5-yl) pentan-2-one (**37**) |  | *E. duttonii* | [45] |
| |  | | |
| (*R*)-5-((*R*,E)-4-Hydroxy-2-methyl-5-(5-oxo-2,5-dihydrofuran-3-yl)pent-2-enyl)-3-methylfuran-2(5H)-one (**38**) | R = OH | *E. homoplastica* | [68] |
| (*R*,E)-4-Methyl-5-((*R*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-1-(5-oxo-2,5-dihydrofuran-3-yl)pent-3-en-2-yl acetate (**39**) | R = OAc | *E. homoplastica* | [68] |
| (*R*,E)-3-Methyl-5-(2-methyl-5-(5-oxo-2,5-dihydrofuran-3-yl)pent-2-enyl)furan-2(5H)-one (40) | R = H | *E. homoplastica* | [68] |
| (*S*,E)-2,6-Dimethyl-9-(5-oxo-2,5-dihydrofuran-3-yl)nona-2,6-dien-4-yl acetate (**41**) |  | *E. forrestii* | [68] |

**Table 5** Structures and distribution of secondary metabolites of *Eremophila*: chemical structures of the isolated cyclic sesquiterpenes

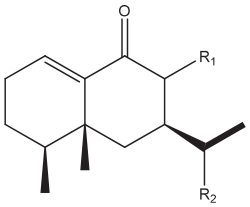
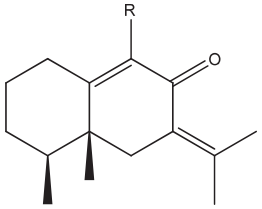
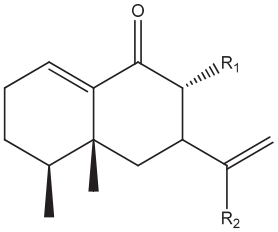
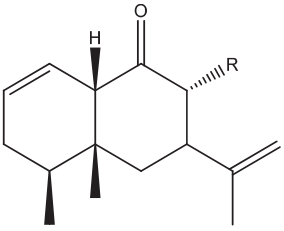
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| |  | | |
| Eremophilone (**42**) | $R_1 = H$; $R_2 = CH_3$ | *E. mitchellii* | [17,28,69] |
| (2*R*,3*R*,4a*R*,5*S*)-2-Hydroxy-3-isopropyl-4a,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2H)-one (**43**) | $R_1 = \alpha$-OH; $R_2 = CH_3$ | *E. mitchellii* | [28,69,79] |
| (*R*)-2-((2*S*,8*S*,8a*R*)-8,8a-Dimethyl-4-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)propanal (**44**) | $R_1 = H$; $R_2 = CHO$ | *E. rotundifolia* | [80] |
| |  | | |
| 9-Hydroxy-7(11),9-eremophiladien-8-one (**45**) | R = OH | *E. mitchellii* | [28,69,79] |
| (4a*R*,5*S*)-4a,5-Dimethyl-3-(propan-2-ylidene)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (**46**) | R = H | *E. mitchellii* | [28,69,79] |
| |  | | |
| (4a*R*,5*S*)-4a,5-Dimethyl-3-(prop-1-en-2-yl)-3,4,4a,5,6,7-hexahydronaphthalen-1(2H)-one (**47**) | $R_1 = H$; $R_2 = CH_3$ | *E. mitchellii* | [17] |
| 2-((8*S*,8a*R*)-8,8a-Dimethyl-4-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)acrylaldehyde (**48**) | $R_1 = H$; $R_2 = CHO$ | *E. mitchellii* | [17] |
| 8-Hydroxy-10,11-eremophiladien-9-one (**49**) | $R_1 = OH$; $R_2 = CH_3$ | *E. mitchellii* | [17] |
| |  | | |

**Table 5** Continued.

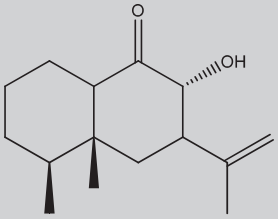
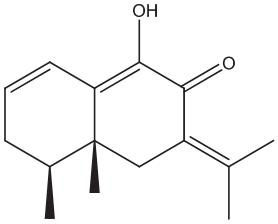
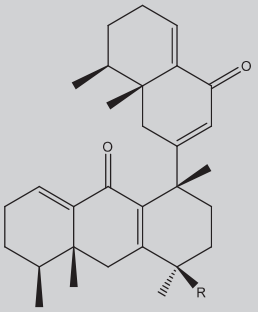
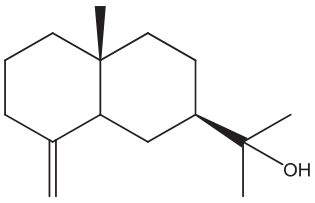
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| 8-Hydroxy-1,11-eremophiladien-9-one (**50**) | R = OH | *E. mitchellii* | [28,69,79] |
| 1,11-Eremophiladien-9-one (**51**) | R = H | *E. mitchellii* | [28,69,79] |
| 8-Hydroxy-11-eremophilen-9-one (santalcamphor) (**52**) |  | *E. mitchellii* | [28,69,79] |
| 9-Hydroxy-1,7(11),9-eremophilatrien-8-one (**53**) |  | *E. mitchellii* | [17] |
| |  | | |
| (4*S*,4a*R*,5*S*,8*S*)-8-((8*S*,8a*R*)-8,8a-Dimethyl-4-oxo-1,4,6,7,8,8a-hexahydronaphthalen-2-yl)-4,4a,5,8-tetramethyl-3,4,4a,5,6,7,8,10-octahydroanthracen-9(2H)-one (**54**) | R = H | *E. mitchellii* | [17] |
| (4*S*,4a*R*,5*R*,8*S*)-8-((8*S*,8a*R*)-8,8a-Dimethyl-4-oxo-1,4,6,7,8,8a-hexahydronaphthalen-2-yl)-5-hydroxy-4,4a,5,8-tetramethyl-3,4,4a,5,6,7,8,10-octahydroanthracen-9(2H)-one (**55**) | R = OH | *E. mitchellii* | [17] |
| β-Eudesmol (**56**) |  | *E. drummondii*<br>*E. cuneifolia*<br>*E. dalyana*<br>*E. flaccida*<br>*E. leucophylla*<br>*E. subfloccosa*<br>*E. scoparia* | [14]<br>[71]<br>[53]<br>[72]<br>[14]<br>[14]<br>[14] |

**Table 5** Continued.

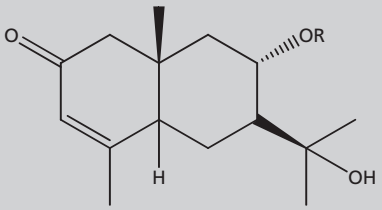
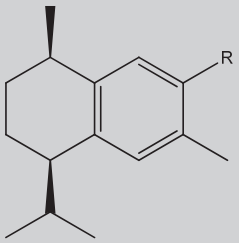
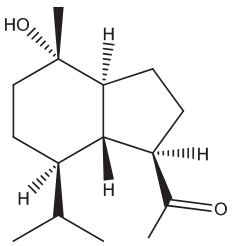
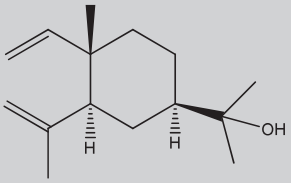
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| |  | | |
| (4a*R*,6*R*,7*S*,8a*S*)-7-Hydroxy-6-(2-hydroxypropan-2-yl)-4,8a-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (**57**) | R = H; 4a = α-H | *E. scoparia* | [70] |
| (2*S*,3*R*,4a*R*,8a*S*)-3-(2-Hydroxypropan-2-yl)-5,8a-dimethyl-7-oxo-1,2,3,4,4a,7,8,8a-octahydronaphthalen-2-yl acetate (**58**) | R = Ac; 4a = α-H | *E. scoparia* | [70] |
| (4a*S*,6*R*,7*S*,8a*S*)-7-Hydroxy-6-(2-hydroxypropan-2-yl)-4,8a-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (**59**) | R = H; 4a = β-H | *E. scoparia* | [70] |
| |  | | |
| (1*R*, 4*R*)-Calamenene (**60**) | R = H | *E. drummondii*<br>*E. virens* | [73]<br>[74] |
| (1*R*, 4*R*)-7-Hydroxy-calamenene (**61**) | R = OH | *E. drummondii*<br>*E. virens* | [73]<br>[74] |
| (+)-Oplopanone (**62**) |  | *E. miniata* | [61] |
| Elemol (**63**) |  | *E. dalyana*<br>*E. flaccida*<br>*E. leucophylla* | [53]<br>[76]<br>[14] |

**Table 5** Continued.

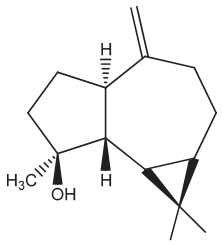
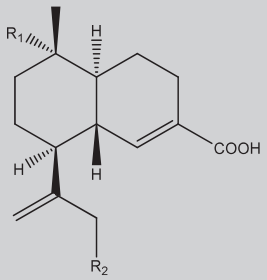
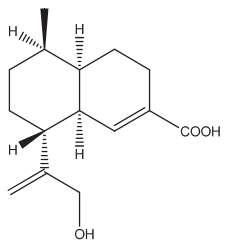
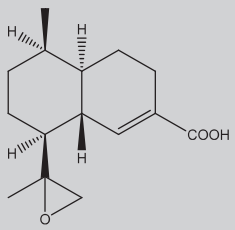
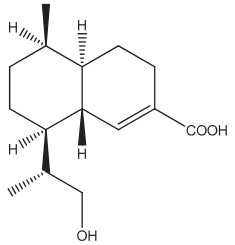
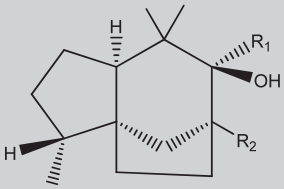
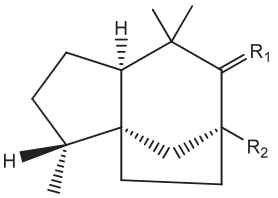
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| Spathulenol (**64**) |  | *E. cuneifolia*<br>*E. paisley*<br>*E. racemosa*<br>*E. drummondii* | [71]<br>[14]<br>[14]<br>[14] |
| |  | | |
| (4a*R*,5*R*,8*S*,8a*R*)-8-(3-Hydroxyprop-1-en-2-yl)-5-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylic acid (**65**) | $R_1$ = H; $R_2$ = OH | *E. virgata*<br>*E. interstans* | [75]<br>[76] |
| (4a*S*,5*S*,8*S*,8a*R*)-5-Hydroxy-5-methyl-8-(prop-1-en-2-yl)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylic acid (**66**) | $R_1$ = OH; $R_2$ = H | *E. interstans* | [76] |
| (4a*R*,5*R*,8*R*,8a*S*)-8-(3-Hydroxyprop-1-en-2-yl)-5-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylic acid (**67**) |  | *E. virgata*<br>*E. interstans* | [75]<br>[76] |
| (4a*R*,5*R*,8*S*,8a*R*)-5-Methyl-8-((*R*)-2-methyloxiran-2-yl)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylic acid (**68**) |  | *E. virgata* | [75] |
| (4a*R*,5*R*,8*S*,8a*S*)-8-((*R*)-1-Hydroxypropan-2-yl)-5-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylic acid (**69**) |  | *E. virgata* | [75] |

**Table 5** Continued.

| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| |  | | |
| **70** | $R_1 = CH_3$; $R_2 = H$ | *E. georgei* | [77,78] |
| | | *E. metallicorum* | [77] |
| | | *E. subteretifolia* | [14] |
| **71** | $R_1 = H$; $R_2 = CH_3$ | *E. georgei* | [77,78] |
| | | *E. metallicorum* | [77] |
| | | *E. subteretifolia* | [14] |
| |  | | |
| Sesquithuriferone (**72**) | $R_1 = O$; $R_2 = CH_3$ | *E. georgei* | [77,78] |
| | | *E. metallicorum* | [77] |
| | | *E. subteretifolia* | [14] |
| | | *E. mitchellii* | [17] |
| **73** | $R_1 = -CH_2$; $R_2 = H$ | *E. georgei* | [77,78] |
| | | *E. metallicorum* | [77] |
| | | *E. subteretifolia* | [14] |

Generally, the calamenenes, which occur in *E. drummondii*, have the (1*R*,4*R*)-configuration; they are closely related to the serrulatanes, which have the (1*R*,4*S*)-configuration.[14]

## Viscidanes

Another group of bicyclic diterpenes which are widespread in *Eremophila* are the viscidanes. The first example (**135**) was isolated from *E. viscida* and presents a carbon skeleton of acorane sesquiterpenes, e.g. α-acoradiene.[14,105,106] Several examples of viscidane diterpenes differing in positions and level of oxidation have been identified from *E. alatisepala*, *E. cuneifolia*, *E. crenulata*, and many others, and all contain an allylic oxygenation in the cyclohexene ring.[52,57,97,98]

## Cedrane isoprenologues

A variety of the highly diverse *E. georgei* complex and *E. gilesii* produce a new class of diterpenes, which contains a new tricyclic skeleton called cedrane.[100] The best example, which is regarded as an isoprenologue of 2-epi-(-)-α-cedrene (**145**), was described in 1986 by Forster *et al.*[99] These diterpenes vary in the degree of oxygenation and unsaturation in the side chain and isomers with exocyclic and endocyclic double bond.

## Decipianes

The decipiane diterpenes also contain a tricyclic carbon skeleton (tricycle [5.3.1.$0^{5,11}$] undecane), which is unique for di- and sesquiterpenes. Like the cedrane-type diterpenes, the decipianes have been isolated from only a few *Eremophila* species. *E. decipiens* contains a complex mixture of decipianes (**149**–**151**), which had been reported by Ghisalberti *et al.*[101] in 1975. The only diterpene present in an extract of *E. clarkei* is the dihydroxy acid derivative of compound **152**.[107] Several varieties of the *E. georgei* complex produce various decipianes also.[14]

## Eremanes

The most complex diterpene skeleton isolated from *Eremophila* is known as 'eremane'. Eremolactone (**154**) was reported from the resin of *E. fraseri* and from the essential

**Table 6** Structures and distribution of secondary metabolites of *Eremophila*: chemical structures of the isolated diterpenes

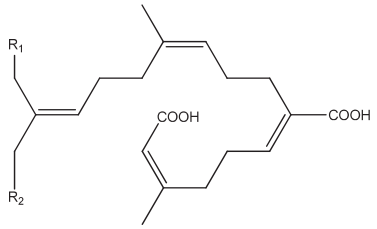
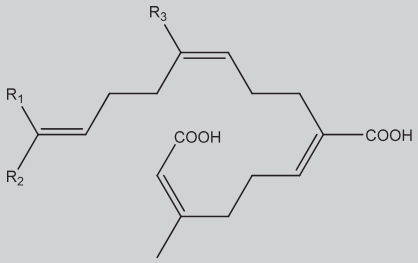
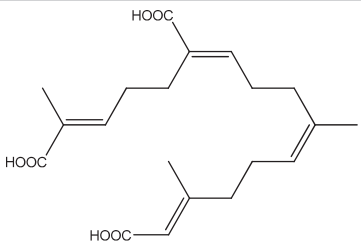
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| |  | | |
| (2E,6Z)-2-((3Z,7Z)-9-Hydroxy-4,8-dimethylnona-3,7-dienyl)-6-methylocta-2,6-dienedioic acid (**74**) | $R_1$ = OH; $R_2$ = H | *E. exilifolia*<br>*E. glutinosa* | [83]<br>[84] |
| (2E,6Z)-2-((3Z,7Z)-9-Acetoxy-4,8-dimethylnona-3,7-dienyl)-6-methylocta-2,6-dienedioic acid (**75**) | $R_1$ = OAc; $R_2$ = H | *E. glutinosa* | [84] |
| (2E,6Z)-2-((3Z,7E)-9-Hydroxy-4,8-dimethylnona-3,7-dienyl)-6-methylocta-2,6-dienedioic acid (**76**) | $R_1$ = H; $R_2$ = OH | *E. exilifolia*<br>*E. glutinosa* | [83]<br>[84] |
| (2E,6Z)-2-((3Z,7E)-9-Acetoxy-4,8-dimethylnona-3,7-dienyl)-6-methylocta-2,6-dienedioic acid (**77**) | $R_1$ = H; $R_2$ = OAc | *E. glutinosa* | [84] |
| |  | | |
| (1Z,5E,9Z,13E)-2,10-Dimethylpentadeca-1,5,9,13-tetraene-1,6,14-tricarboxylic acid (**78**) | $R_1$ = $CH_3$; $R_2$ = COOH; $R_3$ = $CH_3$ | *E. exilifolia* | [83] |
| (1Z,5E,9Z,13Z)-2,10-Dimethylpentadeca-1,5,9,13-tetraene-1,6,14-tricarboxylic acid (79) | $R_1$ = COOH; $R_2$ = $CH_3$; $R_3$ = $CH_3$ | *E. exilifolia* | [83] |
| (1Z,5E,9E,13E)-10-Formyl-2-methylpentadeca-1,5,9,13-tetraene-1,6,14-tricarboxylic acid (**80**) | $R_1$ = $CH_3$; $R_2$ = COOH; $R_3$ = CHO | *E. glutinosa* | [83] |
| (1Z,5E,9E,13E)-2-Methylpentadeca-1,5,9,13-tetraene-1,6,10,14-tetracarboxylic acid (**81**) | $R_1$ = $CH_3$; $R_2$ = COOH; $R_3$ = COOH | *E. glutinosa* | [83] |
| (1E,5Z,9E,13E)-2,6-Dimethylpentadeca-1,5,9,13-tetraene-1,10,14-tricarboxylic acid (**82**) |  | *E. glutinosa* | [83] |

**Table 6** Continued.

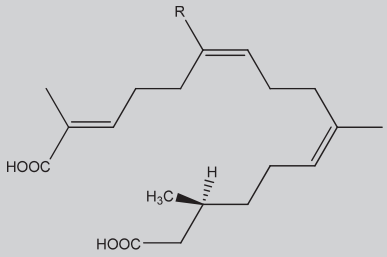
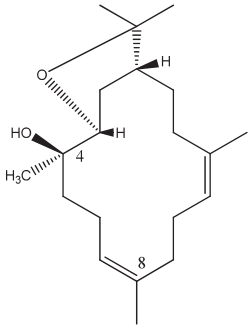
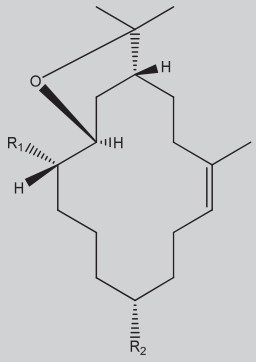
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| |  | | |
| (*S*,5Z,9E,13E)-2,6-Dimethylpentadeca-5,9,13-triene-1,10,14-tricarboxylic acid (**83**) | R = COOH | *E. glutinosa* | [83] |
| (*S*,2E,6E,10Z)-6-Formyl-2,10,14-trimethylhexadeca-2,6,10-trienedioic acid (**84**) | R = CHO | *E. glutinosa* | [83] |
| Epoxycembranediol (**85**) |  | *E. georgei* | [85] |
| |  | | |
| (1*R*,8*R*,12*S*,13*R*,Z)-4,15,15-Trimethyl-14-oxabicyclo[11.2.1]hexadec-4-ene-8,12-dicarboxylic acid (**86**) | $R_1$ = COOH; $R_2$ = COOH | *E. abietina* | [52] |
| (1*R*,8*R*,12*S*,13*R*,Z)-Dimethyl 4,15,15-trimethyl-14-oxabicyclo[11.2.1]hexadec-4-ene-8,12-dicarboxylate (**87)** | $R_1$ = $COOCH_3$; $R_2$ = $COOCH_3$ | *E. abietina* | [52] |
| (1*R*,8*R*,12*S*,13*R*,Z)-8-Formyl-4,15,15-trimethyl-14-oxabicyclo[11.2.1]hexadec-4-ene-12-carboxylic acid (**88**) | $R_1$ = COOH; $R_2$ = CHO | *E. abietina*<br>*E. granitica* | [52] |

**Table 6** Continued.

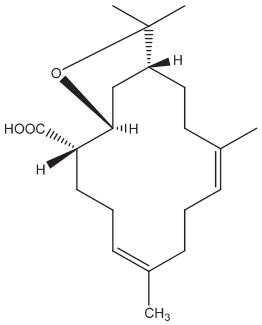
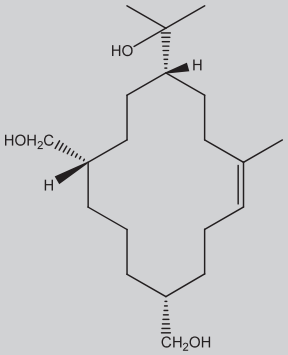
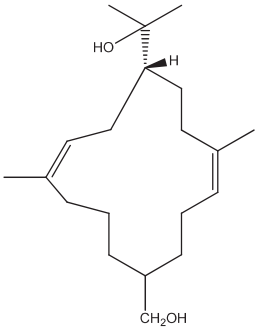
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| The malonate half ester of 3,15-epoxy-19-oxocembra-7,11-dien-18-ol (**89**) | $R_1 = CH_2OCOCH_2COOH$; $R_2 = CHO$ | *E. fraseri*<br>*E. platycalyx* | [54] |
| (1*R*,8*R*,12*R*,13*R*,Z)-12-(Hydroxymethyl)-4,15,15-trimethyl-14-oxabicyclo[11.2.1] hexadec-4-ene-8-carbaldehyde (**90**) | $R_1 = CH_2OH$; $R_2 = CHO$ | *E. platycalyx* | [54] |
| 19-Acetoxy-3,15- epoxycembr-11-en-19-oic acid (**91**) | $R_1 = CH_2OAc$; $R_2 = COOH$ | *E. gilesii* | [14] |
| (1*R*,4*Z*,8*Z*,12*S*,13*R*)-4,8,15,15-Tetramethyl-14-oxabicyclo[11.2.1]hexadeca-4,8-diene-12-carboxylic acid (**92**) |  | *E. granitica* | [52] |
| ((1*S*,5*R*,12*S*,*Z*)-12-(2-Hydroxypropan-2-yl)-9-methylcyclotetradec-8-ene-1,5-diyl)dimethanol (**93**) |  | *E. clarkei* | [86] |
| 2-((1*R*,3*Z*,11*Z*)-8-(Hydroxymethyl)-4,12-dimethylcyclotetradeca-3,11-dienyl)propan-2-ol (**94**) |  | *E. dempsteri* | [54] |

**Table 6** Continued.

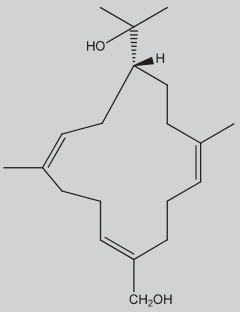
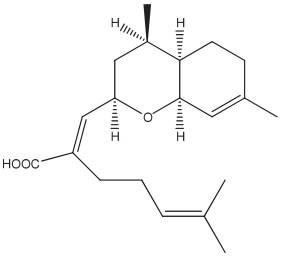
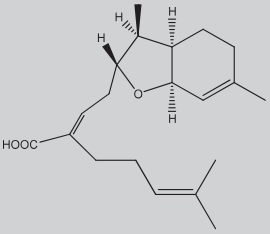
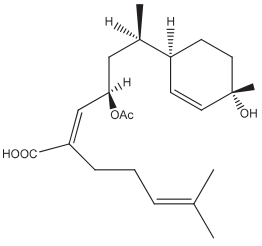
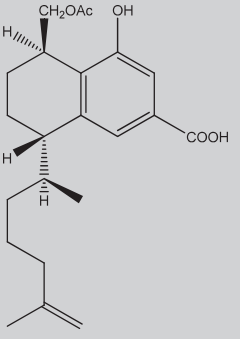
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| 2-((*R*,3Z,7E,11Z)-8-(Hydroxymethyl)-4,12-dimethylcyclotetradeca-3,7,11-trienyl)propan-2-ol (**95**) |  | *E. dempsteri* | [54] |
| 2-((3,4,5,6,8aHexahydro-4,7-dimethyl-2H-1-benzopyran-2-yl)-methylene)-6 methyl-5-heptenoic acid (**96**) |  | *E. foliosissima*<br>*E. gilesii* | [87]<br>[88] |
| (E)-2-(2-((2*R*,3*S*,3a*R*,7a*S*)-3,6-Dimethyl-2,3,3a,4,5,7a-hexahydrobenzofuran-2-yl)ethylidene)-6-methylhept-5-enoic acid (**97**) |  | *E. foliosissima*<br>*E. gilesii* | [87]<br>[88] |
| (4*R*,6*R*,E)-4-Acetoxy-6-((1*R*,4*S*)-4-hydroxy-4-methylcyclohex-2-enyl)-2-(4-methylpent-3-enyl)hept-2-enoic acid (**98**) |  | *E. foliosissima* | [87] |
| (5*R*,8*S*)-5-(Acetoxymethyl)-4-hydroxy-8-((*S*)-6-methylhept-6-en-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**99**) |  | *E. glabra* | [14] |

**Table 6** Continued.

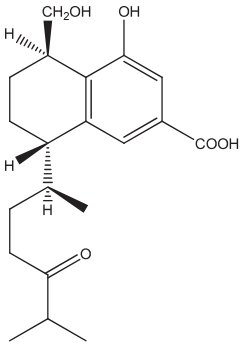
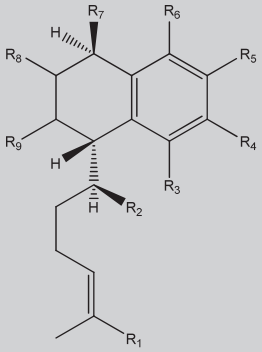
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| (5*R*,8*S*)-4-Hydroxy-5-(hydroxymethyl)-8-((S)-6-methyl-5-oxoheptan-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**100**) |  | *E. virens* | [74] |
| Dihydroxyserrulatic acid (**101**) |  $R_1 = CH_2OH$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_3$; $R_8 = H$; $R_9 = H$ | *E. serrulata* | [89,90] |
| (5*R*,8*S*)-8-((*S*,E)-7-Acetoxy-6-methylhept-5-en-2-yl)-4-hydroxy-5-methyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**102**) | $R_1 = CH_2OAc$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_3$; $R_8 = H$; $R_9 = H$ | *E. serrulata* | [14] |
| 8,19-Dihydroxyserrulat-14-ene (**103**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_2OH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_3$; $R_8 = H$; $R_9 = H$ | *E. neglecta* | [39] |
| 2,19-Diacetoxy-8-hydroxyserrulat-14-ene (**104**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_2OCOCH_3$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_3$; $R_8 = CH_3COO$; $R_9 = H$ | *E. neglecta* | [39] |
| 8-Hydroxyserrulat-14-en-19-oic acid (**105**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_3$; $R_8 = H$; $R_9 = H$ | *E. neglecta* | [39] |
| 8,20-Dihydroxyserrulat-14en-19-oic acid (**106**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_2OH$; $R_8 = H$; $R_9 = H$ | *E. calorhabdos*<br>*E. decipiens*<br>*E. denticulata*<br>*E. glabra*<br>*E. paisley*<br>*E. virens* | [91]<br>[74]<br>[74]<br>[74]<br>[14]<br>[74] |
| 8,20-Diacetoxyserrulat-14-en-19-oic acid (**107**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = OAc$; $R_7 = CH_2OAc$; $R_8 = H$; $R_9 = H$ | *E. glabra*<br>*E. hughesii*<br>*E. serrulata* | [74]<br>[74]<br>[40] |

**Table 6** Continued.

| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| 7,8,20-Trihydroxyserrulat-14-ene (**108**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_3$; $R_5 = OH$; $R_6 = OH$; $R_7 = CH_2OH$; $R_8 = H$; $R_9 = H$ | *E. linearis*<br>*E. granitica*<br>*E. duttonii* | [92]<br>[92]<br>[45] |
| (5*S*,7*S*,8R)-8-(Hydroxymethyl)-3-methyl-5-((*S*)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-1,2,7-triol (**109**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_3$; $R_5 = OH$; $R_6 = OH$; $R_7 = CH_2OH$; $R_8 = \alpha$-OH; $R_9 = H$ | *E. granitica*<br>*E. hughesii* | [92]<br>[74] |
| (5*S*,7*S*,8*R*)-8-(Hydroxymethyl)-3-methyl-5-((*S*)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-1,7-diol (**110**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_3$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_2OH$; $R_8 = \alpha$-OH; $R_9 = H$ | *E. gibsoni* | [74] |
| (*S*)-2-((1*S*,4*R*)-5,8-Dihydroxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-6-methylhept-5-enal (**111**) | $R_1 = CH_3$; $R_2 = CHO$; $R_3 = OH$; $R_4 = CH_3$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_3$; $R_8 = H$; $R_9 = H$ | *E. rotundifolia* | [65] |
| ((1*R*,4*S*)-8-Hydroxy-4-((*S*)-6-methylhept-5-en-2-yl)-1,2,3,4-tetrahydronaphthalene-1,6-diyl)dimethanol (**112**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_2OH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_2OH$; $R_8 = H$; $R_9 = H$ | *E. falcata* | [76] |
| (5*S*,8*R*)-5-((*S*)-1-Hydroxy-6-methylhept-5-en-2-yl)-3,8-dimethyl-5,6,7,8-tetrahydronaphthalen-1-ol (**113**) | $R_1 = CH_3$; $R_2 = CH_2OH$; $R_3 = H$; $R_4 = CH_3$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_3$; $R_8 = H$; $R_9 = H$ | *E. flaccida* | [76] |
| 3,8-Dihydroxyserrulatic acid (**114**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_3$; $R_8 = H$; $R_9 = \alpha$-OH | *E. sturtii* | [12] |
| 20-Acetoxy-8-hydroxyserrulat-14-en-19-oic acid (**115**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_2OAc$; $R_8 = H$; $R_9 = H$ | *E. serrulata* | [40] |
| 8,20-Dihydroxyserrulat-14-en-19-oic acid (**116**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = OH$; $R_7 = CH_2OH$; $R_8 = H$; $R_9 = H$ | *E. serrulata* | [40] |
| (3*R*)-Serrulat-14-ene-3,7,8,20-tetraol (**117**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_3$; $R_5 = OH$; $R_6 = OH$; $R_7 = CH_2OH$; $R_8 = H$; $R_9 = \alpha$-OH | *E. duttonii* | [93] |
| Serrulatic acid (**118**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = COOH$; $R_5 = H$; $R_6 = H$; $R_7 = CH_3$; $R_8 = H$; $R_9 = H$ | *E. sturtii* | [12] |
| (5*S*,6*R*,8*R*)-8-(Hydroxymethyl)-3-methyl-5-((*S*)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-1,6-diol (**119**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_3$; $R_5 = H$; $R_6 = OH$; $R_7 = \beta$-$CH_2OH$; $R_8 = H$; $R_9 = \alpha$-OH | *E. phyllopoda'* | [94] |
| (5*S*,6*R*,8*S*)-8-(Hydroxymethyl)-3-methyl-5-((*S*)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-1,6-diol (**120**) | $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_3$; $R_5 = H$; $R_6 = OH$; $R_7 = \alpha$-$CH_2OH$; $R_8 = H$; $R_9 = \alpha$-OH | *E. phyllopoda'* | [94] |

**Table 6** Continued.

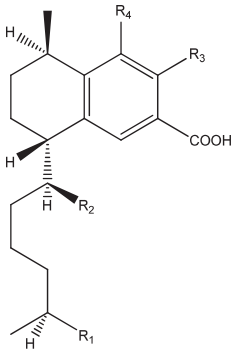
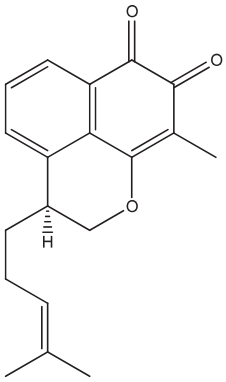
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| |  | | |
| (5*R*,8*S*)-8-((2*S*,6*S*)-1,7-Dihydroxy-6-methylheptan-2-yl)-3,4-dihydroxy-5-methyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**121**) | $R_1 = CH_2OH$; $R_2 = CH_2OH$; $R_3 = OH$; $R_4 = OH$ | *E. drummondii* *E. woolsiana* | [74] |
| (5*R*,8*S*)-8-((2*S*,6*S*)-1-Acetoxy-7-hydroxy-6-methylheptan-2-yl)-3,4-dihydroxy-5-methyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**122**) | $R_1 = CH_2OH$; $R_2 = CH_2OAc$; $R_3 = OH$; $R_4 = OH$ | *E. drummondii* *E. woolsiana* | [74] |
| (5*R*,8*S*)-8-((2*S*,6*S*)-1,7-Diacetoxy-6-methylheptan-2-yl)-3,4-dihydroxy-5-methyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**123**) | $R_1 = CH_2OAc$; $R_2 = CH_2OAc$; $R_3 = OH$; $R_4 = OH$ | *E. drummondii* *E. woolsiana* | [74] |
| (5*R*,8*S*)-8-((2*S*,6*S*)-7-Hydroxy-6-methylheptan-2-yl)-5-methyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**124**) | $R_1 = CH_2OH$; $R_2 = CH_3$; $R_3 = H$; $R_4 = H$ | *E. biserrata* | [74] |
| (5*R*,8*S*)-3,4-Dihydroxy-8-((2*S*,6*S*)-7-hydroxy-6-methylheptan-2-yl)-5-methyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**125**) | $R_1 = CH_2OH$; $R_2 = CH_3$; $R_3 = OH$; $R_4 = OH$ | *E. drummondii* | [92] |
| 9-Methyl-3-(4-methyl-3-pentenyl)-2,3-dihydronaphtho[1,8-bc]pyran-7,8-dione (*o*-naphthoquinone) (**126**) |  | *E. serrulata* | [40] |

**Table 6** Continued.

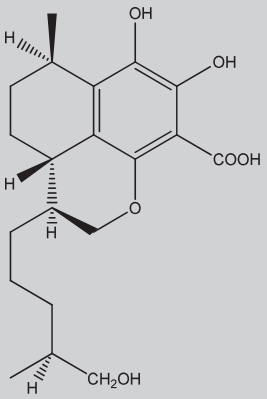
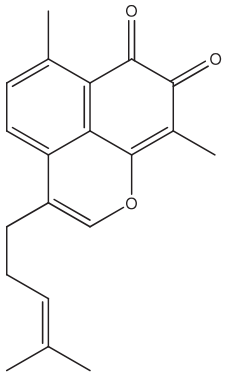
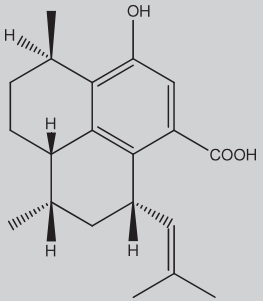
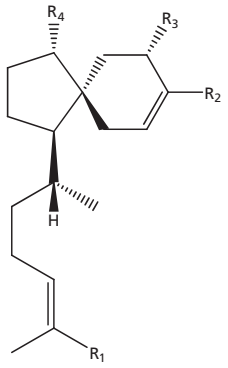
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| (3*S*,3a*S*,6*R*)-7,8-Dihydroxy-3-((*S*)-5-hydroxy-4-methylpentyl)-6-methyl-2,3,3a,4,5,6-hexahydrobenzo[de]chromene-9-carboxylic acid (**127**) |  | *E. drummondii* | [74] |
| Biflorin (**128**) |  | *E. latrobei* | [74] |
| Cycloserrulatane (**129**) |  | *E. serrulata* | [95] |
| |  | | |
| 5α-Hydroxyviscida-3,l4-dien-20-oic acid (**130**) | $R_1 = CH_3$; $R_2 = COOH$; $R_3 = OH$; $R_4 = CH_3$ | *E. viscida*<br>*E. gilesii*<br>*E. cuneifolia* | [96]<br>[14]<br>[57] |

**Table 6** Continued.

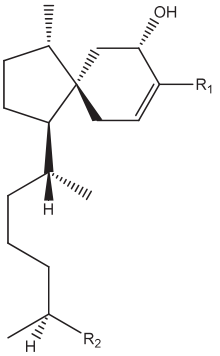
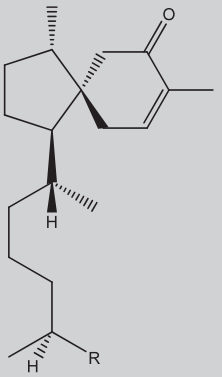
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| (*R*,E)-6-((1*R*,4*S*,5*S*,9*S*)-9-Hydroxy-4,8-dimethylspiro[4.5]dec-7-en-1-yl)-2-methylhept-2-enoic acid (**131**) | $R_1$ = COOH; $R_2$ = $CH_3$; $R_3$ = OH; $R_4$ = $CH_3$ | *E. punctata* | [97] |
| (*R*,E)-Methyl 6-((1R,4S,5S,9S)-9-hydroxy-4,8-dimethylspiro[4.5]dec-7-en-1-yl)-2-methylhept-2-eneperoxoate (**132**) | $R_1$ = $COOOCH_3$; $R_2$ = $CH_3$; $R_3$ = OH; $R_4$ = $CH_3$ | *E. punctata* | [97] |
| (1*S*,4*R*,5*R*,9*S*)-9-Hydroxy-1-(hydroxymethyl)-4-((*R*)-6-methylhept-5-en-2-yl)spiro[4.5]dec-7-ene-8-carboxylic acid (**133**) | $R_1$ = $CH_3$; $R_2$ = COOH; $R_3$ = OH; $R_4$ = $CH_2$ OH | *E. crenulata*<br>*E. exotrachys*<br>*E. platythamnos*<br>*E. gibsoni* | [98]<br>[98]<br>[98]<br>[14] |
| (1*S*,4*R*,5*R*,9*S*)-9-Hydroxy-8-methyl-4-((*R*)-6-methylhept-5-en-2-yl)spiro[4.5]dec-7-ene-1-carboxylic acid (**134**) | $R_1$ = $CH_3$; $R_2$ = $CH_3$; $R_3$ = OH; $R_4$ = COOH | *E. alatisepala* | [98] |
| |  | | |
| (1*R*,4*S*,5*S*,9*S*)-9-Hydroxy-1-((2*R*,6*S*)-7-hydroxy-6-methylheptan-2-yl)-4-methylspiro[4.5]dec-7-ene-8-carboxylic acid (**135**) | $R_1$ = COOH; $R_2$ = $CH_2OH$ | *E. viscida*<br>*E. cuneifolia* | [96]<br>[57] |
| (1*R*,4*S*,5*S*,7*S*)-1-((2*R*,6*S*)-7-Hydroxy-6-methylheptan-2-yl)-4,8-dimethylspiro[4.5]dec-8-en-7-ol (**136**) | $R_1$ = $CH_3$; $R_2$ = $CH_2OH$ | *E. verticilata* | [97] |
| (2*S*,6*R*)-6-((1*R*,4*S*,5*S*,9*S*)-9-Hydroxy-4,8-dimethylspiro[4.5]dec-7-en-1-yl)-2-methylheptyl acetate (**137**) | $R_1$ = $CH_3$; $R_2$ = $CH_2OAc$ | *E. verticilata* | [97] |
| (2*S*,6*R*)-6-((1*R*,4*S*,5*S*,9*S*)-9-Hydroxy-4,8-dimethylspiro[4.5]dec-7-en-1-yl)-2-methylheptanoic acid (**138**) | $R_1$ = $CH_3$; $R_2$ = COOH | *E. verticilata* | [97] |
| |  | | |

**Table 6** Continued.

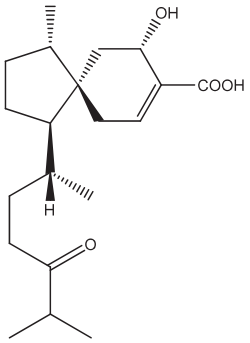
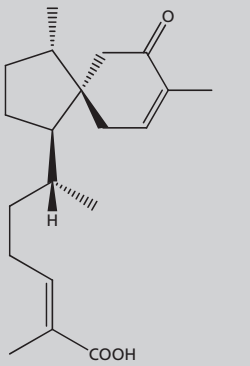
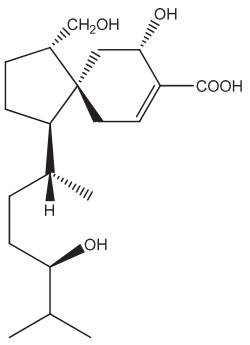
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| (1*R*,4*S*,5*S*)-1-((2*R*,6*S*)-7-Hydroxy-6-methylheptan-2-yl)-4,8-dimethylspiro[4.5]dec-8-en-7-one (**139**) | R = $CH_2OH$ | *E. verticilata* | [97] |
| (2*S*,6*R*)-6-((1*R*,4*S*,5*S*)-4,8-Dimethyl-9-oxospiro[4.5]dec-7-en-1-yl)-2-methylheptanoic acid (**140**) | R = COOH | *E. verticilata* | [97] |
| (1*S*,4*R*,5*S*,9*S*)-9-Hydroxy-1-methyl-4-((*R*)-6-methyl-5-oxoheptan-2-yl)spiro[4.5]dec-7-ene-8-carboxylic acid (**141**) |  | *E. cuneifolia* | [71] |
| (*R*,E)-6-((1*R*,4*S*,5*S*)-4,8-Dimethyl-9-oxospiro[4.5]dec-7-en-1-yl)-2-methylhept-2-enoic acid (**142**) |  | *E. punctata* | [97] |
| (1*R*,4*S*,5*R*,9*S*)-9-Hydroxy-1-((2*R*,5*R*)-5-hydroxy-6-methylheptan-2-yl)-4-(hydroxymethyl) spiro[4.5]dec-7-ene-8-carboxylic acid (**143**) |  | *E. cuneifolia* | [71] |

**Table 6** Continued.

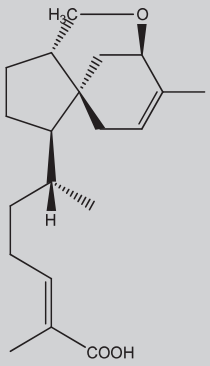
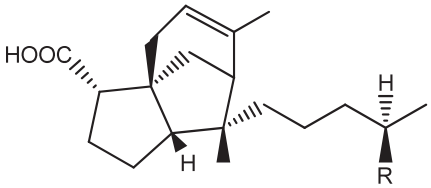
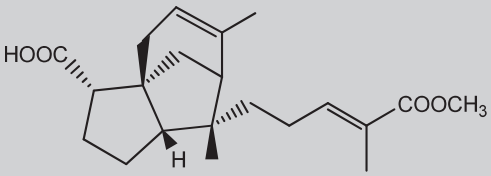
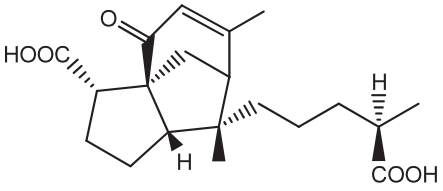
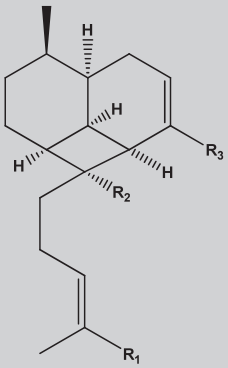
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| (*R*,E)-6-((1*R*,4*S*,5*S*,9*R*)-9-Methoxy-4,8-dimethylspiro[4.5]dec-7-en-1-yl)-2-methylhept-2-enoic acid (**144**) |  | *E. (new species)* | [98] |
| |  | | |
| **145** | R = $CH_2OH$ | *E. georgei* | [99] |
| **146** | R = COOH | *E. 'pungens'* | [100] |
| **147** |  | *E. georgei* | [88,99] |
| **148** |  | *E. 'pungens'* | [100] |
| |  | | |
| (E)-5-((1*R*,1a*S*,1a1*R*,4*R*,4a*R*,7a*S*)-1-(Hydroxymethyl)-4,7-dimethyl-1a,1a1,2,3,4,4a,5,7a-octahydro-1H-cyclobuta[de]naphthalen-1-yl)-2-methylpent-2-enoic acid (**149**) | $R_1$ = COOH; $R_2$ = $CH_2OH$; $R_3$ = $CH_3$ | *E. decipiens* | [101,102] |

**Table 6** Continued.

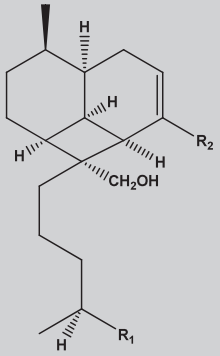
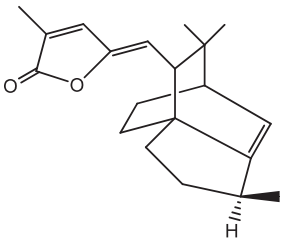
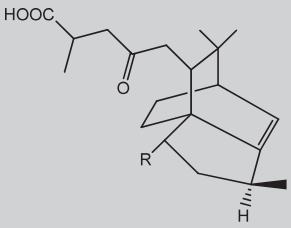
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| (E)-5-((1*R*,1a*S*,1a1*R*,4*R*,4a*R*,7a*S*)-1,7-Bis(hydroxymethyl)-4-methyl-1a,1a1,2,3,4,4a,5,7a-octahydro-1H-cyclobuta[de]naphthalen-1-yl)-2-methylpent-2-enoic acid (**150**) | $R_1$ = COOH; $R_2$ = $CH_2OH$; $R_3$ = $CH_2OH$ | *E. decipiens* | [101,102] |
| ((1*R*,1a*S*,1a1*R*,4a*R*,5*R*,7a*S*)-1-((E)-5-Hydroxy-4-methylpent-3-enyl)-5-methyl-1a,1a1,4,4a,5,6,7,7a-octahydro-1H-cyclobuta[de]naphthalene-1,2-diyl)dimethanol (**151**) | $R_1$ = $CH_2OH$; $R_2$ = $CH_2OH$; $R_3$ = $CH_2OH$ | *E. decipiens* | [101,102] |
| |  | | |
| (1*R*,1a*R*,1a1*R*,4a*R*,5*R*,7a*S*)-1-((*S*)-5-Hydroxy-4-methylpentyl)-1-(hydroxymethyl)-5-methyl-1a,1a1,4,4a,5,6,7,7a-octahydro-1H-cyclobuta[de]naphthalene-2-carboxylic acid (**152**) | $R_1$ = $CH_2OH$; $R_2$ = COOH | *E. clarkei* | [103] |
| (*S*)-5-((1*R*,1a*S*,1a1*R*,4*R*,4a*R*,7a*S*)-1,7-Bis(hydroxymethyl)-4-methyl-1a,1a1,2,3,4,4a,5,7a-octahydro-1H-cyclobuta[de]naphthalen-1-yl)-2-methylpentanoic acid (**153**) | $R_1$ = COOH; $R_2$ = $CH_2OH$ | *E. georgei* | [14] |
| Eremolactone (**154**) |  | *E. freelingii*<br>*E. fraseri* | [82]<br>[81] |
| |  | | |
| **155** | R = H | *E. fraseri* | [104] |
| **156** | R = α-OH | *E. fraseri* | [104] |

**Table 6** Continued.

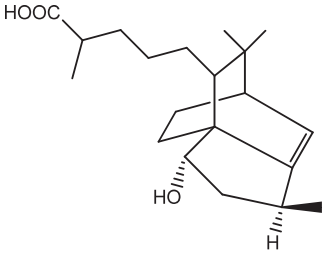
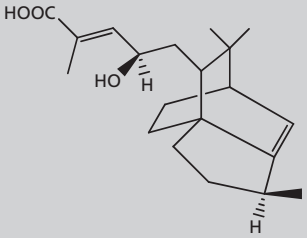
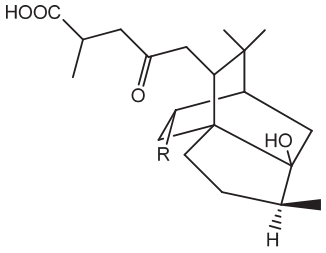
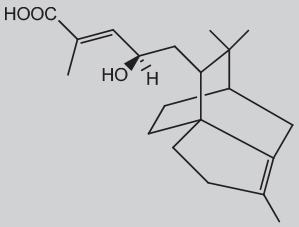
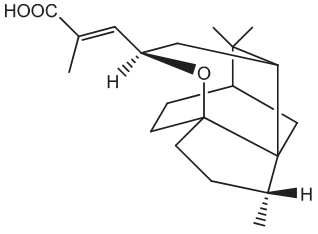
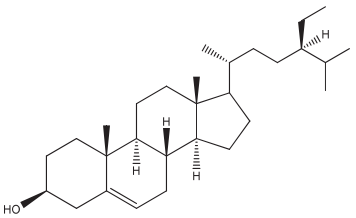
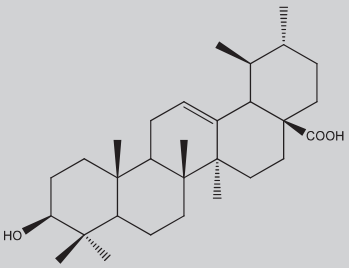
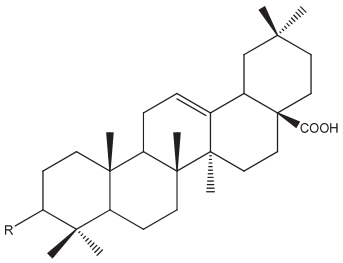
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| **157** |  | *E. macmillaniana* | [72] |
| 16-Hydroxyerema-5,17-dien-19-oic acid (**158**) |  | *E. fraseri*<br>*E. gilesii* | [104]<br>[14] |
| |  | | |
| 5β-Hydroxy-16-oxoereman-19oic acid (**159**) | R = H | *E. cuneifolia*<br>*E. spectabilis* | [57] |
| **160** | R = OH | *E. fraseri* | [104] |
| **161** |  | *E. fraseri* | [104] |
| **162** |  | *E. fraseri* | [104] |

**Table 7** Structures and distribution of secondary metabolites of *Eremophila*: chemical structures of the isolated sterols and triterpenes

| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| β-Sitosterol (**163**) |  | *E. mitchellii*<br>*E. georgei* | [69]<br>[14] |
| Ursolic acid (**164**) |  | *E. caerulea* | [14] |
| |  | | |
| Oleanolic acid (**165**) | R = β-OH | *E. caerulea* | [14] |
| 3-Epi-oleanolic acid (**166**) | R = α-OH | *E. platycalyx* | [54] |

oil of *E. freelingii*.[14,82] Isoeremanes and their cyclic ethers were isolated from *E. fraseri*.[14]

## Sterols and triterpenes

These terpenoids with a C27 and C30 skeleton are not accumulated to any significant extent in the genus *Eremophila*. The only sterol definitively identified so far is the ubiquitous phytosterol, β-sitosterol (**163**) in *E. mitchellii* and *E. georgei*.[14,69] Triterpenes also rarely occur and only three have been isolated, such as ursolic (**164**) and oleanolic acid (**165**) from *E. caerulea* and 3-epi-oleanolic acid (**166**) from *E. platycalyx* (Table 7).[14,54]

## Fatty acids

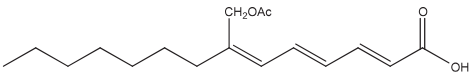
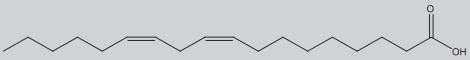
*E. oppositifolia* contains a branched threefold unsaturated fatty acid (**167**) accompanied by smaller amounts of stearic (**168**), oleic and palmitic acid (**169**) and esters of n-hexanoic (**170**), n-heptanoic (**171**), and n-octanoic acid (**172**).[108,109] In most cases superficial analysis of the fats and fatty acids isolated from the resin has failed to reveal other than the usual fatty acids (Table 8).[52]

## Phenolic compounds

The groups of phenolics include flavonoids, which occur widely in *Eremophila* species and they are represented by several polyhydroxylated flavonols and flavones.[14,84,110] They include a flavone dihydroflavonol such as pinobanksin (**186**) and a dihydroflavanol acetate. Flavonoids often contribute a significant portion to the *Eremophila* resins but limited effort has been invested in their identification.

Another group of compounds that arise from the shikimic acid pathway are the lignans. The first representative was dimethyl syringaresinol (**191**) from *E. glabra*.[81] Other lignans include phillyrin (**190**) from *E. racemosa*, a new dihydroxylignan from *E. dalyana*, (+)-epieudesmin (**193**) and (+)-methylxanthoxylol (**194**) from *E. calorhabdos*.[53,74,91]

**Table 8** Structures and distribution of secondary metabolites of *Eremophila*: chemical structures of the isolated fatty acids

| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| Branched triply unsaturated fatty acid (**167**) |  | *E. oppositifolia* | [108] |
| $CH_3$-$(CH_2)_n$-COOH | | | |
| Stearic acid (**168**) | n = 16 | *E. oppositifolia* | [109] |
| Palmitic acid (**169**) | n = 14 | *E. oppositifolia* | [109] |
| n-Hexanoic acid (**170**) | n = 4 | *E. oppositifolia* | [109] |
| n-Heptanoic acid (**171**) | n = 5 | *E. oppositifolia* | [109] |
| n-Octanoic acid (**172**) | n = 6 | *E. oppositifolia* | [109] |
| Linoleic acid (**173**) |  | *E. oppositifolia* | [109] |
| | $CH_3$-$(CH_2)_n$-CH = CH-$(CH_2)_7$-COOH | | |
| Oleic acid (**174**) | n = 6 | *E. oppositifolia* | [109] |
| Palmitoleic acid (**175**) | n = 5 | *E. abietina* | [52] |

In addition, other aromatic phenylpropanoids such as safrole (**176**) and eugenol methyl ether (**177**) have been identified in *E. longifolia* (Table 9).[111]

### Miscellaneous compounds

The most common representative of this class of compound is the polyalcohol mannitol (**200**). It has been isolated or detected in a number of *Eremophila* species including *E. fraseri*, *E. leucophylla* and *E. ramosissima*.[14,81]

Cyanogenic glucosides, such as the β-glucoside prunasin (**199**), are less common. Prunasin represents the cyanogenic toxic principle of *E. maculata*, which has been termed Poison bush because of its toxins.[14] The caffeoyl ester and disaccharide verbascoside (**197**) has recently been isolated from *E. georgei* and *E. cuneifolia*.[14] Another caffeoyl ester is poliumoside (**198**), which has been found in Lamiaceae.[112]

A number of *Eremophila* species were tested with a simple assay system for the presence of alkaloids. Amongst those showing positive results were *E. bignoniiflora, E. longifolia, E. maculata* and *E. mitchellii* (Table 9).[14,113]

## Current State and Prospects

Natural products are promising candidates for drug discovery and they still continue to play an important role in future small organic compound drug development programs.[114] In this context, the typical drug discovery process relies mainly on medium and high-throughput bioassay screening platforms to find promising candidates for a particular target. Reports on pharmacological effects of medicinal plants are growing almost exponentially. However, it is very difficult to attribute the pharmacological activity in a multi-component mixture, as in plant extracts consisting of a diversity of secondary metabolites, to only a single compound of an extract.[50] There is good evidence that the secondary metabolites, present in a mixture, exhibit additive or even synergistic effects. Such properties are hardly detected by high-throughput screening assays. Secondary metabolites are able to interfere with many molecular targets in the cells. From the data mentioned above it is clear that the composition of an *Eremophila* extract would be determined by the method of preparation. Given the reported methods, it seems likely that the extracts would have been mixtures of lipophilic and hydrophilic materials. Also, it is obvious that the majority of *Eremophila* species exhibit promising antimicrobial activity, which may be attributed to their high diterpene content. These lipophilic secondary metabolites can dissolve in biomembranes resulting in disturbance of the close interaction between membrane lipids and proteins, thus changing the conformation of membrane proteins. These membrane proteins include ion channels, transporters for nutrients and intermediates, receptors, and proteins of signal transduction, and the cytoskeleton.[115] A change of protein conformation usually leads to a loss of function. Moreover, at higher concentrations, these secondary metabolites interact with the lipophilic inner core of biomembranes represented by fatty acids and cholesterol leading to disturbance of the membrane fluidity. This type of interaction between the secondary metabolites and the biomembranes could explain the antimicrobial, antiviral and cytotoxic effects of many *Eremophila* preparations. Also, the serrulatane diterpenes found in many *Eremophila* species as *E. duttonii, E. latrobei* and *E. paisley* are structurally related to a group of potent anti-inflammatory compounds isolated from sea whips.[6] Verbascoside isolated so far from certain *Eremophila* species and which may occur more commonly in other *Eremophila* species is of some pharmacological interest. It exhibits

**Table 9** Structures and distribution of secondary metabolites of *Eremophila*: chemical structures of the isolated phenylpropanoids, flavonoids, lignans, caffeoyl ester, cyanogenic glucosides and mannitol

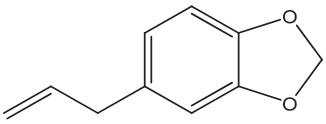
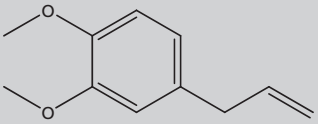
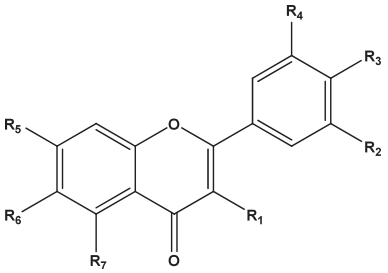
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| Safrole (**176**) |  | *E. longifolia* | [111] |
| Eugenol methyl ether (**177**) |  | *E. longifolia* | [111] |
| |  | | |
| Galangin-3-methyl ether (**178**) | $R_1 = OCH_3$; $R_2 = H$; $R_3 = H$; $R_4 = H$; $R_5 = OH$; $R_6 = H$; $R_7 = OH$ | *E. alternifolia* | [81] |
| 5,7-Dihydroxy-3-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**179**) | $R_1 = OCH_3$; $R_2 = H$; $R_3 = OCH_3$; $R_4 = H$; $R_5 = OH$; $R_6 = H$; $R_7 = OH$ | *E. clarkei* | [14] |
| 5,7-Dihydroxy-3,6-dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**180**) | $R_1 = OCH_3$; $R_2 = H$; $R_3 = OCH_3$; $R_4 = H$; $R_5 = OH$; $R_6 = OCH_3$; $R_7 = OH$ | *E. clarkei* | [14] |
| 3′,5,5′-Trihydroxy-3,4′,6,7tetramethoxyflavone (**181**) | $R_1 = OCH_3$; $R_2 = OH$; $R_3 = OCH_3$; $R_4 = OH$; $R_5 = OCH_3$; $R_6 = OCH_3$; $R_7 = OH$ | *E. fraseri* | [14,81] |
| 5,7-Dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**182**) | $R_1 = H$; $R_2 = H$; $R_3 = OCH_3$; $R_4 = H$; $R_5 = OH$; $R_6 = H$; $R_7 = OH$ | *E. inflata* | [14] |
| 5,6,7-Trihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**183**) | $R_1 = H$; $R_2 = H$; $R_3 = OCH_3$; $R_4 = H$; $R_5 = OH$; $R_6 = OH$; $R_7 = OH$ | *E. decipiens* | [14] |
| 5,7-Dihydroxy-6-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**184**) | $R_1 = H$; $R_2 = H$; $R_3 = OCH_3$; $R_4 = H$; $R_5 = OH$; $R_6 = OCH_3$; $R_7 = OH$ | *E. decipiens* | [14] |
| 4′,7Dimethoxy-5-hydroxyflavone (**185**) | $R_1 = H$; $R_2 = H$; $R_3 = OCH_3$; $R_4 = H$; $R_5 = OCH_3$; $R_6 = H$; $R_7 = OH$ | *E. homoplastica* | [68] |

**Table 9** Continued.

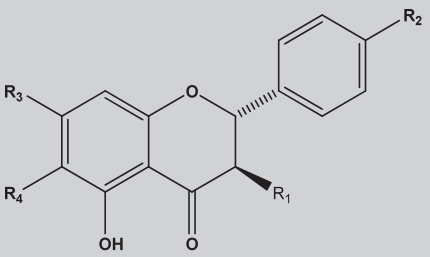
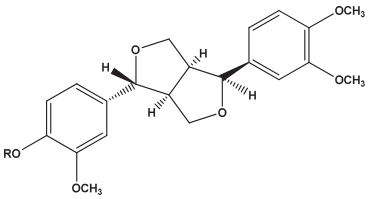
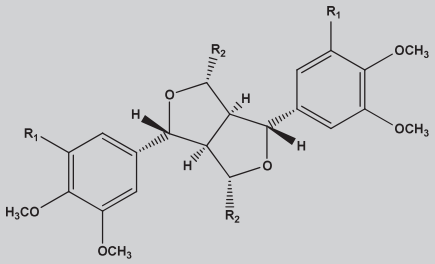
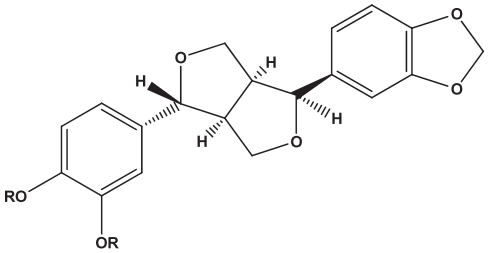
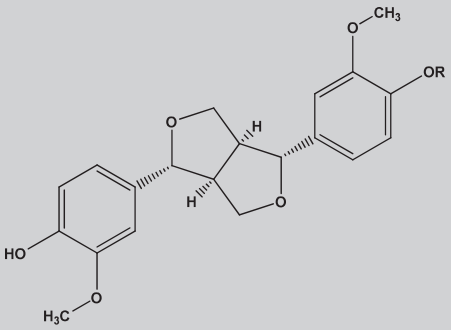
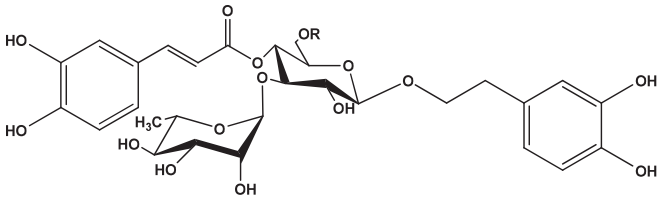
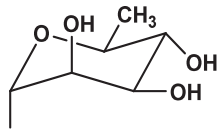
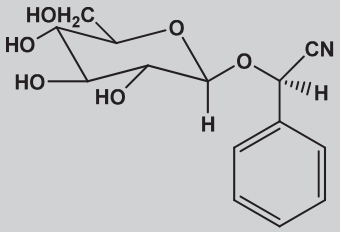
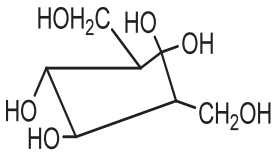
| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| |  | | |
| Pinobanksin (**186**) | $R_1$ = OH; $R_2$ = H; $R_3$ = OH; $R_4$ = H | *E. alternifolia*<br>*E. flaccida*<br>*E. romoissima* | [81]<br>[72]<br>[81] |
| (*S*)-5,7-Dihydroxy-2-phenylchroman-4-one (**187**) | $R_1$ = H; $R_2$ = H; $R_3$ = OH; $R_4$ = H | *E. flaccida*<br>*E. exotrachys* | [72]<br>[72,113] |
| (2*R*,3*R*)-5-Hydroxy-2-(4-hydroxyphenyl)-7-methoxy-4-oxochroman-3-yl acetate (**188**) | $R_1$ = OAc; $R_2$ = OH; $R_3$ = $CH_3O$; $R_4$ = H | *E. glutinosa* | [84] |
| (2*R*,3*R*)-5,7-Dihydroxy-2-(4-hydroxyphenyl)-6-methoxy-4-oxochroman-3-yl acetate (**189**) | $R_1$ = OAc; $R_2$ = OH; $R_3$ = OH; $R_4$ = $CH_3O$ | *E. glutinosa* | [84] |
| Phillyrin (**190**) |  <br>R = α-D-glucose | *E. racemosa* | [74] |
| |  | | |
| Dimethyl syringaresinol (**191**) | $R_1$ = $OCH_3$; $R_2$ = H | *E. glabra* | [91] |
| 3,6-Bis-(3,4-dimethoxyphenyl)-tetrahydro-1H,3H-furo(3,4c)furan-1,4-diol (dihydroxy lignan) (**192**) | $R_1$ = H; $R_2$ = OH | *E. dalyana* | [53] |
| |  | | |
| (+)-Epieudesmin (**193**) | R = $CH_3$ | *E. calorhabdos* | [91] |
| (+)-Methylxanthoxylol (**194**) | R = -$CH_2$- | *E. calorhabdos* | [91] |

**Table 9** Continued.

| Compound name (No.) | Structure | Species | References |
|---|---|---|---|
| |  | | |
| (+)-Pinoresinol (**195**) | R = H | *E. maculata* | [56] |
| (+)-Pinoresinol 4′-glucoside (**196**) | R = Glucose | *E. maculata* | [56] |
| |  | | |
| Verbascoside (**197**) | R = H | *E. georgei*<br>*E. cuneifolia* | [14] |
| Poliumoside (**198**) | R =  | *E. gilesii* | [112] |
| Prunasin (**199**) |  | *E. maculata* | [14] |
| Alditol mannitol (**200**) |  | *E. fraseri*<br>*E. leucophylla*<br>*E. ramosissima* | [81]<br>[14]<br>[81] |

antihypertensive and analgesic activity, and potentiates anti-tremor L-dopa activity in animals. Furthermore, it shows antimicrobial, immunosuppressive and antitumour activity.[116]

## Prospects

Since the use of medicinal plants is a widely accepted therapeutic strategy for millions of people, further attention should be focused on the discovery of the exact modes of action of their extracts as well as the isolated pure compounds and potential combinations. However, because of the diverse molecular pharmacological data, the spectrum of interpretation and speculations seem to be endless. The observations described above provide some circumstantial leads and raise a number of questions that must be taken into consideration. The major one is the nature and biological activity of the more polar compounds present in

different *Eremophila* species, which must be of a great interest. Also, authentication of all the drugs should be undertaken carefully by chemical fingerprinting or DNA barcoding to ensure the quality of the drug and hence the corresponding biological activity. Finally, studies on standardization of the drug and preclinical trials are required for an integration and acceptance of many *Eremophila* extracts in conventional medicine.

## Conclusions

The Australian endemic genus *Eremophila* offers a wide range of ethnobotanical utilizations, which are based on the diverse patterns of secondary metabolites. The main secondary metabolites are terpenoids, ranging from monoterpenes, iridoid glucosides, sesquiterpene, diterpenes, steroids and triterpenes, and phenolics (mainly flavonoids, lignans and phenylpropanoids). A rich diversity of structures is visible within sesqui- and diterpenes. Phenolics and terpenoids contribute to the pharmacological properties of *Eremophila* extracts and isolated secondary metabolites, such as cardiotonic, anti-inflammatory, antimicrobial and cytotoxic activities.

## Declarations

### Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

### Funding

This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## References

1. Van Wyk B-E, Wink M. *Medicinal Plants of the World: An Illustrated Scientific Guide to Important Medicinal Plants and Their Uses*. Portland, OR: Timber Press, 2004.
2. Mabberley DJ. *Mabberley's Plant-Book: A Portable Dictionary of Plants, Their Classification and Uses*. Cambridge: Cambridge University Press, 2008.
3. Richmond GS, Ghisalberti EL. The Australian desert shrub *Eremophila* (myoporaceae): medicinal, cultural, horticultural and phytochemical uses. *Econ Bot* 1994; 48: 35–59.
4. Kadereit JW. *Flowering Plants, Dicotyledons: Lamiales (except Acanthaceae Including Avicenniaceae)*. New York: Springer-Verlag, 2004.
5. Judd WS. *Plant Systematics: A Phylogenetic Approach*. Sunderland: Sinauer Associates, 2008.
6. Ghisalberti EL. The ethnopharmacology and phytochemistry of *Eremophila* species (Myoporaceae). *J Ethnopharmacol* 1994; 44: 1–9.
7. Diaz AM *et al*. Phenylpropanoid glycosides from *Scrophularia scorodonia*: in vitro anti-inflammatory activity. *Life Sci* 2004; 74: 2515–2526.
8. Akdemir Z *et al*. Bioassay-guided isolation of anti-inflammatory, antinociceptive and wound healer glycosides from the flowers of *Verbascum mucronatum* Lam. *J Ethnopharmacol* 2011; 136: 436–443.
9. Tasdemir D *et al*. Anti-protozoal and plasmodial FabI enzyme inhibiting metabolites of *Scrophularia lepidota* roots. *Phytochemistry* 2005; 66: 355–362.
10. Jeong EJ *et al*. KD-501, a standardized extract of *Scrophularia buergeriana* has both cognitive-enhancing and antioxidant activities in mice given scopolamine. *J Ethnopharmacol* 2009; 121: 98–105.
11. Singab AN *et al*. Hepatoprotective effect of flavonol glycosides rich fraction from Egyptian *Vicia calcarata* Desf. against $CCl_4$-induced liver damage in rats. *Arch Pharm Res* 2005; 28: 791–798.
12. Liu Q *et al*. Bactericidal and cyclooxygenase inhibitory diterpenes from *Eremophila sturtii*. *Phytochemistry* 2006; 67: 1256–1261.
13. Afifi MSA *et al*. Cytotoxic flavonolignans and flavones from *Verbascum sinaiticum* leaves. *Phytochemistry* 1993; 34: 839–841.
14. Ghisalberti EL. The phytochemistry of the myoporaceae. *Phytochemistry* 1993; 35: 7–33.
15. Tomlinson S, Palombo EA. Characterisation of antibacterial Australian medicinal plant extracts by investigation of the mechanism of action and the effect of interfering substances. *J Basic Microbiol* 2005; 45: 363–370.
16. Semple SJ *et al*. Screening of Australian medicinal plants for antiviral activity. *J Ethnopharmacol* 1998; 60: 163–172.
17. Beattie KD *et al*. Chemical composition and cytotoxicity of oils and eremophilanes derived from various parts of *Eremophila mitchellii* Benth. (Myoporaceae). *Phytochemistry* 2011; 72: 400–408.
18. Rogers KL *et al*. Inhibition of platelet aggregation and 5-HT release by extracts of Australian plants used traditionally as headache treatments. *Eur J Pharm Sci* 2000; 9: 355–363.
19. Maiden JH. *The Useful Native Plants of Australia (Including Tasmania)*. Melbourne, Vic.: Trubner and Co., 1889.
20. Webb LJ. The use of plant medicines and poisons by Australian aborigines. *Mankind* 1969; 7: 137–146.
21. Barr A. *Traditional Bush Medicines: An Aboriginal Pharmacopoeia. Aboriginal Communities of the Northern Territory of Australia*. Richmond,Vic.: Greenhouse Publications, 1988.
22. Low T. *Bush Medicine: A Pharmacopoeia of Natural Remedies*. North Ryde, NSW: Angus and Robertson, 1990.
23. Latz PK. *Bushfires & Bushtucker. Aboriginal Plant Use in Central Aus-*

*tralia*. Alice Springs, NT: IAD Press, 1995.
24. Clarke PA. *Aboriginal People and Their Plants*. Dural, NSW: Rosenberg Publishing, 2011.
25. Barr A. *Traditional Aboriginal Medicines in the Northern Territory of Australia*. Darwin: Conservation Commission of the Northern Territory of Australia, 1993.
26. Silberbauer GB. Ecology of the ernabella aboriginal community. *Anthropol Forum* 1971; 3: 21–36.
27. O'Connell JF *et al.* Traditional and modern plant use among the Alyawara of central Australia. *Econ Bot* 1983; 31: 80–109.
28. Bradfield AE *et al.* The constitution of eremophilone and of two related hydroxy-ketones from the wood oil of *Eremophila mitchellii*. *J Chem Soc* 1932; 2744–2759.
29. Palombo EA, Semple SJ. Antibacterial activity of Australian plant extracts against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). *J Basic Microbiol* 2002; 42: 444–448.
30. Owen RJ, Palombo EA. Anti-listerial activity of ethanolic extracts of medicinal plants, *Eremophila alternifolia* and *Eremophila duttonii*, in food homogenates and milk. *Food Control* 2007; 18: 387–390.
31. Pennacchio M *et al.* Cardioactive effects of *Eremophila alternifolia* extracts. *J Ethnopharmacol* 1995; 47: 91–95.
32. Pennacchio M *et al.* Cardioactive compounds from *Eremophila* species. *J Ethnopharmacol* 1996; 53: 21–27.
33. Pennacchio M *et al.* Interesting biological activities from plants traditionally used by Native Australians. *J Ethnopharmacol* 2005; 96: 597–601.
34. Meilak M, Palombo EA. Antimycobacterial activity of extracts derived from Australian medicinal plants. *Res J Microbiol* 2008; 7: 535–538.
35. Shah A *et al.* Identification of the antibacterial component of an ethanolic extract of the Australian medicinal plant, *Eremophila duttonii*. *Phytother Res* 2004; 18: 615–618.
36. Palombo EA, Semple SJ. Antibacterial activity of traditional Australian medicinal plants. *J Ethnopharmacol* 2001; 77: 151–157.
37. Hayhoe EJ, Palombo EA. Extracts of *Eremophila longifolia* inhibit the cariogenic activities of *Streptococcus mutans* and *Streptococcus sobrinus*. *J Med Plants Res* 2011; 5: 2476–2482.
38. Sweeney AP *et al.* Xanthine oxidase inhibitory activity of selected Australian native plants. *J Ethnopharmacol* 2001; 75: 273–277.
39. Ndi CP *et al.* Antimicrobial compounds from the Australian desert plant *Eremophila neglecta*. *J Nat Prod* 2007; 70: 1439–1443.
40. Ndi CP *et al.* Antimicrobial compounds from *Eremophila serrulata*. *Phytochemistry* 2007; 68: 2684–2690.
41. Pennacchio M *et al.* The effect of verbascoside on cyclic 3′,5′-adenosine monophosphate levels in isolated rat heart. *Eur J Pharmacol* 1996; 305: 169–171.
42. Willerson JT *et al.* Improvement in myocardial function and coronary blood flow in ischemic myocardium after mannitol. *J Clin Invest* 1972; 51: 2988–2999.
43. Fixler DE *et al.* Effect of hypertonic mannitol and isoproterenol on regional coronary flow following right ventriculotomy. *Circulation* 1976; 54: 26–31.
44. Surh Y-J, Packer L. *Oxidative Stress, Inflammation, and Health*. Boca Raton, FL: Taylor & Francis, 2005.
45. Smith JE *et al.* Identification of antibacterial constituents from the indigenous Australian medicinal plant *Eremophila duttonii* F. Muell. (Myoporaceae). *J Ethnopharmacol* 2007; 112: 386–393.
46. Ndi CP *et al.* Instability of antibacterial serrulatane compounds from the Australian plant species *Eremophila duttonii*. *Aust J Chem* 2012; 65: 20–27.
47. Anakok OF *et al.* Antibacterial spectrum and cytotoxic activities of serrulatane compounds from the Australian medicinal plant *Eremophila neglecta*. *J Appl Microbiol* 2012; 112: 197–204.
48. Wink M *et al.* Secondary metabolites from plants inhibiting ABC transporters and reversing resistance of cancer cells and microbes to cytotoxic and antimicrobial agents. *Front Microbiol* 2012; 3: 130–145.
49. Ndi CP *et al.* Antimicrobial activity of some Australian plant species from the genus *Eremophila*. *J Basic Microbiol* 2007; 47: 158–164.
50. Wink M. Evolutionary advantage and molecular modes of action of multicomponent mixtures used in phytomedicine. *Curr Drug Metab* 2008; 9: 996–1009.
51. Russell AD. Mechanisms of antimicrobial action of antiseptics and disinfectants: an increasingly important area of investigation. *J Antimicrob Chemother* 2002; 49: 597–599.
52. Ghisalberti EL *et al.* The chemistry of *Eremophila* spp. XIX. New cembrane diterpenes from *E. granitica* and *E. abietina*. *Aust J Chem* 1983; 36: 1187–1196.
53. Ghisalberti EL *et al.* The chemistry of *Eremophila* spp. XXVII. A new lignan from *E. dalyana*. *Aust J Chem* 1987; 40: 405–411.
54. Ghisalberti EL *et al.* The chemistry of *Eremophila* spp. XXV. New cembrene derivatives from *E. dempsteri*, *E. platycalyx* and *E. fraseri*. *Aust J Chem* 1986; 39: 1703–1710.
55. Smith J *et al.* Intraspecific variation in essential oil composition of *Eremophila longifolia* F. Muell. (Myoporaceae): evidence for three chemotypes. *Phytochemistry* 2010; 71: 1521–1527.
56. Syah YM, Ghisalberti EL. Biologically active cyanogenetic, iridoid and lignan glycosides from *Eremophila maculata*. *Fitoterapia* 1996; 67: 447–451.
57. Croft KD *et al.* The chemistry of *Eremophila* spp. XXI. Structural study of a new eremane diterpene. *Aust J Chem* 1984; 37: 785–793.
58. Hegarty BF *et al.* Terpenoid chemistry. XVII. (-)-Ngaoine, a toxic constituent of *Myoporum deserti*. The absolute configuration of (-)-

Ngaione. *Aust J Chem* 1970; 23: 107–117.
59. Dimitriadis E, Massy-Westropp R. The structure of eremoacetal, a sesquiterpene from *Eremophila rotundifolia*. *Aust J Chem* 1979; 32: 2003–2015.
60. Blackburne ID *et al*. Terpenoid chemistry XX. Myoporone and dehydromyoporone, toxic furanoid ketones from *Myoporum* and *Eremophila* species. *Aust J Chem* 1972; 25: 1787–1796.
61. Dastlik KA *et al*. Sesquiterpenes from *Eremophila* species. *Phytochemistry* 1989; 28: 1425–1426.
62. Massy-Westropp RA *et al*. Freelingyne, an acetylenic sesquiterpenoid. *Tetrahedron Lett* 1966; 7: 1939–1946.
63. Ingham CF *et al*. A synthesis of freelingyne. *Aust J Chem* 1974; 27: 1477–1489.
64. Knight DW, Pattenden G. Freelingnite, a new furanosesquiterpene from *Eremophila freelingii*. *Tetrahedron Lett* 1975; 16: 1115–1116.
65. Abell AD *et al*. The structure of a stable serrulatane diterpenoid acetal from *Eremophila rotundifolia*. *Aust J Chem* 1985; 38: 1837–1845.
66. Dimitriadis E, Massy-Westropp R. Furanosesquiterpenes from *Eremophila rotundifolia*. *Aust J Chem* 1980; 33: 2729–2736.
67. Sutherland MD, Rodwell JL. Terpenoid chemistry. XXVIII. Furanosesquiterpene β-ketols from *Myoporum betcheanum*, *M. deserti*, *M. montanum* and other Myoporaceae. *Aust J Chem* 1989; 42: 1995–2019.
68. Syah YM *et al*. Three new sesquiterpene butenolides from *Eremophila* species. *J Nat Prod* 1997; 60: 49–51.
69. Massy-Westropp RA, Reynolds GD. Eremophilane sesquiterpenes from *Eremophila mitchellii*. *Aust J Chem* 1966; 19: 303–307.
70. Babidge PJ, Massy-Westropp RA. New eudesmane sesquiterpenoids from *Eremophila scoparia*. *Aust J Chem* 1984; 37: 629–633.
71. Ghisalberti E *et al*. The chemistry of *Eremophila* spp. XX. The absolute stereochemistry of the viscidane diterpenes. *Aust J Chem* 1984; 37: 635–647.
72. Ghisalberti EL *et al*. Diterpenes from *Eremophila* species. *Phytochemistry* 1990; 29: 316–318.
73. Croft KD *et al*. Absolute configuration of the (+)-calamenenes: crystal structure of 7-hydroxycalamenene. *J Chem Soc, Perkin Trans* 1978; 1: 1267–1270.
74. Forster PG *et al*. Serrulatane diterpenes from *Eremophila* spp. *Phytochemistry* 1986; 25: 1377–1383.
75. Ghisalberti EL *et al*. A new stereochemical class of bicyclic sesquiterpenes from *Eremophila virgata* W.V. Fitzg. (Myoporaceae). *Tetrahedron* 1989; 45: 6297–6308.
76. Ghisalberti EL *et al*. A sesquiterpene acid from *Eremophila interstans*. *Phytochemistry* 1990; 29: 2700–2701.
77. Carrol PJ *et al*. Tricyclic sesquiterpenes from *Eremophila georgei*. *Phytochemistry* 1976; 15: 777–780.
78. Ghisalberti EL *et al*. Crystal structure and absolute configuration of 2α, 6, 6, 8-tetramethyltricyclo [6.2. 1.0] undecan-7β-yl p-bromobenzoate. *J Chem Soc, Perkin Trans* 1976; 2: 1300–1303.
79. Chetty GL, Zalkow LH. 7a (H)-Eremophila-1, 11-dien-9-one. A new sesquiterpene of the eremophilane type. *Tetrahedron Lett* 1969; 10: 307–309.
80. Adell AD, Massy-Westropp RA. Eremophilane and serrulatane terpenoids from *Eremophila rotundifolia*. *Aust J Chem* 1985; 38: 1263–1269.
81. Jefferies PR *et al*. The chemistry of *Eremophila* species. IV. Some flavonoid constituents. *Aust J Chem* 1962; 15: 532–537.
82. Birch AJ *et al*. A possible structure for eremolactone, a new type of diterpene. *J Chem Soc* 1963; 0: 2412–2417.
83. Ghisalberti EL *et al*. The chemistry of *Eremophila* spp. XV. New acyclic diterpenes from *Eremophila* spp. *Aust J Chem* 1981; 34: 1491–1499.
84. Dastlik KA, Ghisalberti EL. Dihydroflavonol sweeteners and diterpenens from *Eremophila glutinosa*. *Fitoterapia* 1992; 63: 523–525.
85. Ghisalberti EL *et al*. The chemistry of *Eremophila* spp. VII: An epoxycembradienol from *Eremophila georgei*. *Tetrahedron* 1977; 33: 3295–3299.
86. Coates P *et al*. The chemistry of *Eremophila* spp. VIII. A cembrenetriol from *E. clarkei*. *Aust J Chem* 1977; 30: 2717–2721.
87. Forster PG *et al*. A new class of monocyclic diterpenes from kraenzlin (Myoporaceae). *Tetrahedron* 1987; 43: 2999–3007.
88. Forster PG *et al*. A new cedrene isoprenologue from the resin of *Eremophila georgei*. *J Nat Prod* 1993; 56: 147–152.
89. Croft KD *et al*. The chemistry of Eremophilaspp–VI*: Stereochemistry and crystal structure of dihydroxyserrulatic acid. *Tetrahedron* 1977; 33: 1475–1480.
90. Croft KD *et al*. The absolute configuration of dihydroxyserrulatic acid. *Aust J Chem* 1979; 32: 2079–2083.
91. Bytheway IR *et al*. The chemistry of *Eremophila* spp. XXIX. The absolute configuration of (+)-syringaresinol dimethyl ether. *Aust J Chem* 1987; 40: 1913–1917.
92. Croft KD *et al*. The chemistry of *Eremophila* spp. XVI. New serrulatanes from *Eremophila* spp. *Aust J Chem* 1981; 34: 1951–1957.
93. Tippett LM, Massy-Westropp RA. Serrulatane diterpenes from *Eremophila duttonii*. *Phytochemistry* 1993; 33: 417–421.
94. Syah YM, Ghisalberti EL. Serrulatane diterpenes from a new *Eremophila* species. *Phytochemistry* 1997; 45: 1479–1482.
95. Ghisalberti EL. A tricyclic diterpene from *Eremophila serrulata*. *Phytochemistry* 1992; 31: 2168–2169.
96. Ghisalberti EL *et al*. The chemistry of *Eremophila* spp. XVIII. A new class of diterpenes from *Eremophila viscida*. *Aust J Chem* 1983; 36: 993–1000.
97. Forster PG *et al*. Viscidane diterpenes from *Eremophila* species. *Phytochemistry* 1993; 32: 1225–1228.
98. Forster PG *et al*. The chemistry of *Eremophila* spp. XXVI. New visci-

dane diterpenes. *Aust J Chem* 1986; 39: 2111–2120.
99. Forster PG *et al*. A new class of tricyclic diterpenes from diels (myoporaceae). *Tetrahedron* 1986; 42: 215–221.
100. Syah YM, Ghisalberti EL. Cedrene isoprenologues from a new *Eremophila* species. *Phytochemistry* 1996; 41: 859–861.
101. Ghisalberti EL *et al*. A new class of diterpenes from *Eremophila* decipiens. *Tetrahedron Lett* 1975; 16: 1775–1778.
102. Maslen EN *et al*. Crystal structure of the tricyclic diterpene derivative 18-hydroxydecipia-2(4),14-dien-1-oic acid. *J Chem Soc, Perkin Trans* 1976; 2: 263–266.
103. Roussis V *et al*. New anti-inflammatory pseudopterosins from the marine octocoral *Pseudopterogorgia elisabethae*. *J Org Chem* 1990; 55: 4916–4922.
104. Carroll PJ *et al*. The chemistry of *Eremophila* spp. XXII. New eremane diterpenes from *E. fraseri*. *Aust J Chem* 1985; 38: 1351–1363.
105. Tomita B, Hirose Y. Terpenoids. XXVI Acoradiene and acorenol, key intermediates of cedrane group sesquiterpenoids, and their transformation into (−)-α-cedrene. *Tetrahedron Lett* 1970; 11: 143–144.
106. Marshall JA *et al*. The chemistry of spiro (4.5) decane sesquiterpenes. *Fortschr Chem Org Naturst* 1974; 31: 283–376.
107. Croft KD *et al*. The chemistry of *Eremophila* spp. XII. A new decipiene diterpene. *Aust J Chem* 1980; 33: 1529–1536.
108. Jefferies PR, Knox JR. The chemistry of *Eremophila* species. 2. A novel unsaturated fatty acid from *Eremophila oppositifolia* R. *Br Aust J Chem* 1961; 14: 628–636.
109. Ghisalberti EL *et al*. Biosynthesis of (2E,4E,6E)-5-acetoxymethyltetra deca-2,4,6-trienoic acid in *Eremophila oppositifolia*. *Phytochemistry* 1979; 18: 65–69.
110. Dell B. Convesion of mevalonic acid by tissue cultures and leaves of *Eremophila fraseri* F. Muell. (Myoporaceae). *Aust J Bot* 1978; 26: 1–7.
111. Della EW, Jefferies PR. The chemistry of *Eremophila* species. III. The essential oil of *Eremophila longifolia* F. Muell. *Aust J Chem* 1961; 14: 663–664.
112. Grice ID *et al*. Isolation of two phenylethanoid glycosides from *Eremophila gilesii*. *J Ethnopharmacol* 2003; 86: 123–125.
113. Stork G, Clarke FH. Cedrol: stereochemistry and total synthesis. *J Am Chem Soc* 1961; 83: 3114–3125.
114. Newman DJ *et al*. Natural products as sources of new drugs over the period 1981–2002. *J Nat Prod* 2003; 66: 1022–1037.
115. Ashour ML, Wink M. Genus Bupleurum: a review of its phytochemistry, pharmacology and modes of action. *J Pharm Pharmacol* 2011; 63: 305–321.
116. Herbert J *et al*. Verbascoside isolated from *Lantana camara*, an inhibitor of protein kinase C. *J Nat Prod* 1991; 54: 1595–1600.