Chapter 13
Baccharis Terpenoid Compounds

Sérgio Ricardo Ambrósio, Mário Ferreira Conceição Santos, Larissa Costa Oliveira, Ana Lúcia Bassi, Jairo Kenupp Bastos, and Rodrigo Cassio Sola Veneziani

Abstract *Baccharis* is an important genus of the Asteraceae family comprising more than 440 species, which are used in folk medicine for displaying important biological activities, such as analgesic, anti-inflammatory, antimicrobial, insect antifeedant, and antiparasitic, among others. There are several classes of metabolites produced by *Baccharis*, from which terpenoid stands out. The main volatile terpenes found in forty *Baccharis* species are reported in this chapter, pointing out *B. dracunculifolia*, the botanical source of green propolis, that contains (E)-nerolidol and spathulenol as major compounds, among others, giving the characteristic smell of green propolis. The combination of gas chromatography coupled with mass spectrometry is a powerful tool for the analyses of essential oils combined with the use of the Kovats index to determine the retention indexes using a homologous series of aliphatic hydrocarbons. Regarding diterpenes in *Baccharis* species, three main carbon skeleton types, kaurane, labdane, and neo-clerodane, have been reported. Many of these diterpenes display antimicrobial, antiparasitic, anti-inflammatory, analgesic, and cytotoxic activities, but the feeding-deterrent potential against insects displayed by neo-clerodane type-diterpenes stands out. In the final part, it is mentioned the triterpene and steroids, which are also found in this genus, and play important role in the reported biological activities of *Baccharis* species, as well as the occurrence of baccharinoids, a particular type of macrocyclic trichothecenes, which are associated with cattle poisoning in South America fed with *B. megapotamica*, but also display antiviral, anticancer, antimalarial, and antifungal activities.

Keywords Chemical structure · Nerolidol · Plant chemistry · Terpenes · Spathulenol

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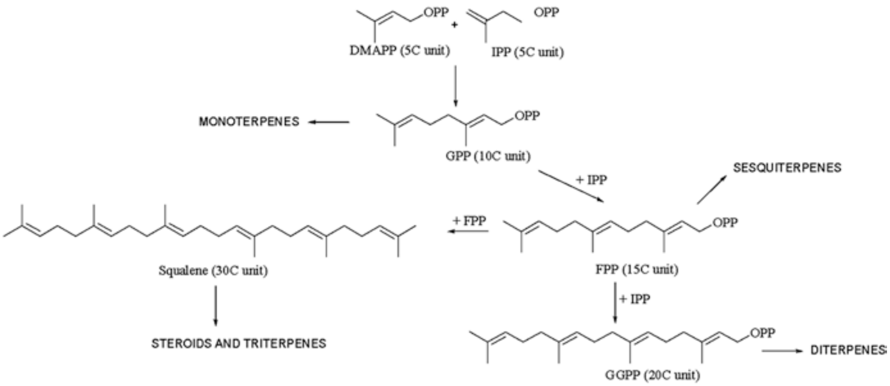


Fig. 13.1 Precursor units of different terpenoids, formed according to the number of isoprene units

1 General Aspects of Terpenes

Terpenoids are a large class of metabolites that can be subdivided according to the number of connected isoprenes (5C) units. Biosynthetically, such units are mostly bonded in a "head-to-tail" sequence in order to furnish the different types of terpenes. The dimethylallyl diphosphate (DMAPP) binds with an isopentenyl diphosphate (IPP) unit to form the 10C unit precursor of monoterpenes (GPP; geranyl diphosphate) [1] (Fig. 13.1). A GPP unit can be subsequently condensed with another IPP group to give farnesyl diphosphate (FPP), the precursor of sesquiterpenes. The addition of another IPP to FPP can furnish the 20C precursor of diterpenes – a geranylgeranyl diphosphate (GGPP) molecule. All these reactions are catalyzed by their respective *trans*-prenyl transferases. Alternatively, the junction of two FPP and two GGPP groups in a "head-to-head" binding can furnish a 30C squalene unit, and a 40C tetraterpene unit, which are the precursors of steroids/triterpenes and carotenoids, respectively (Veneziani et al. 2017; Furtado et al. 2017).

In this chapter, the main types of terpenoids found in *Baccharis* species are reported. Additionally, these compounds are discussed regarding their biological perspectives, focusing on their ecological, pharmacological, and toxicological reported data. Details on the chemical structures of some terpenes and their features are presented, as well.

2 *Baccharis* Essential Oils

Essential oils (EOs; or volatile oils) can be defined as mixtures of volatile and lipophilic, often odoriferous, substances produced by aromatic plants (Furtado et al. 2017). They are associated with a series of important ecological purposes, like molecular signaling among plants and pollinizers, as chemical defensives against predators (insects and other animals), as growth inhibitors of plants, and also as an antimicrobial against fungi or bacteria (Campos et al. 2016; Furtado et al. 2017). Also, these oils are obtained through steam distillation and are utilized in the manufacture of various products such as cosmetics, household cleaning products, air fresheners, and hygiene products, as well as in aromatherapy and in some paramedicinal practices due to their characteristic odor and flavor (Xavier et al. 2013; Campos et al. 2016).

Chemically, EOs are characterized by the presence of phenylpropanoids and relatively low molecular weight terpenoids like monoterpenes and sesquiterpenes. Monoterpenes (10C) present a great variety of structures, such as acyclic chains, monocyclic or aromatic derivatives, and even rigid bicyclic rings (Sarah et al. 2014; Furtado et al. 2017). Sesquiterpenes (15C) are less volatile than monoterpenes, and they can be found in the composition of many essential oils, including commercial ones (Campos et al. 2016; Veneziani et al. 2017) (Fig. 13.2).

The combination of gas chromatography coupled with mass spectrometry (GC-MS) is a powerful tool to analyze EOs in a fast, reliable, and simple way. The use of long capillary columns (up to 60 m) allows the separation of very complex mixtures of volatile compounds (Furtado et al. 2017). Also, this technique presents another important advantage when compared with other methods like thin layer and liquid chromatography, since the use of MS detection allows the identification of the components without the need of analytical standards. This is possible due to (Veneziani et al. 2017) the use of Kovats index as a more accurate form to determine the retention indexes using a homologous series of aliphatic hydrocarbons and (Furtado et al. 2017) the comparison between the mass spectra obtained for each compound and with those present in computational spectral databases (Shibamoto 1987; Furtado et al. 2017; Adams 2017).

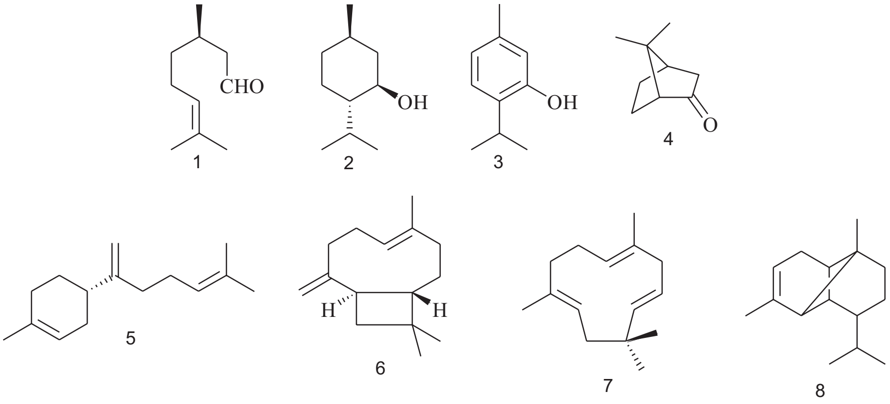


Fig. 13.2 Examples of monoterpenes (**1**-citronellal from *Cymbopogon citratus* "lemongrass", **2**-menthol from *Mentha piperita* "peppermint," **3**- thymol from *Thymus vulgaris* "Thyme," and **4**-camphor from *Rosmarinus officinalis* "Rosemary") and sesquiterpenes from *Copaifera sp.* "Copaíba" oilresins (**5**- β-bisabolene, **6**- *trans*-β-caryophyllene, **7**- α-humulene, and **8**- α-copaene)

Due to the above-mentioned features, GC-MS is broadly used to determine the qualitative and quantitative composition of essential oils of many species of aromatic plants, including the *Bachharis* genus. In this sense, it is possible to find in the literature a great number of studies that present the composition of many EOs of *Baccharis* species. However, for the purposes of this chapter, the focus will be kept on the terpenoids content of such products (Zunino et al. 1998; Albuquerque et al. 2004; Xavier et al. 2013). *Baccharis* species that had their EOs main monoterpenes and sesquiterpenes analyzed using GC-MS and their respective references are displayed in Table 13.1, as well as their chemical structures in Figs. 13.3a and 13.3b.

Table 13.1 *Baccharis* essential oils and their main terpenoids (mono and sesquiterpenes)

Specie	Compounds	References
B. anomala	Alpha-acorenol, spathulenol, caryophyllene oxide, limonene, alpha-thujene, alpha-pinene, sabinene, beta-pinene, myrcene, *p*-cymene, (E)-beta-ocimene, gamma-terpinene, alpha-cadinol, and beta-selinene	Budel et al. (2012), Xavier et al. (2013), and Trombin-Souza et al. (2017)
B. articulata	Spathulenol, palustrol, beta-pinene, beta-caryophyllene, caryophyllene oxide, (E)-nerolidol, and bicyclogermacrene	Zunino et al. (1998), Zunino et al. (2004), Florao et al. (2012), and Tischer et al. (2017)
B. axillaris	Limonene, alpha-thujene, alpha-pinene, sabinene, beta-pinene, myrcene, *p*-cymene, (E)-beta-ocimene, gamma-terpinene, spathulenol, and alpha-cadinol	Trombin-Souza et al. (2017)
B. calvescens	Alpha-thujene, alpha-pinene, sabinene, beta-pinene, myrcene, *p*-cymene, limonene, (E)-beta-ocimene, gamma-terpinene, spathulenol, and alpha-cadinol	Trombin-Souza et al. (2017)
B. caprariaefolia	Beta-caryophyllene, germacrene D, alpha-selinene, and spathulenol	Besten et al. (2012)
B. cordobensis	*Trans*-nerolidol, tau-cadinol, and cubenol	Zunino et al. (2000)
B. coridifolia	Isocaryophyllene, beta-caryophyllene, caryophyllene oxide, beta-selinene, spathulenol, viridiflorol, carotol, and alpha-bisabolol	Bailac et al. (2001), and Besten et al. (2012)
B. darwinii	Limonene, thymol, and 4-terpineol	Kurdelas et al. (2012)
B. dracunculifolia	Beta-caryophyllene, beta-humulene, germacrene D, beta-guaiene, delta-cadinene, (E)-nerolidol, spathulenol, limonene, bicyclogermacrene, beta-elemene, and mustakone	Fabiane et al. (2008), Lago et al. (2008), Parreira et al. (2010), Besten et al. (2012), Florao et al. (2012), Lage et al. (2015), and Salazar et al. (2018)
B. elaeagnoides	Viridiflorol, spathulenol, beta-caryophyllene, and germacrene D	Sayuri et al. (2010)

(continued)

Table 13.1 (continued)

Specie	Compounds	References
B. elaeoides	Gamma-cadinene, limonene, tau-cadinol, alpha-cadinol, beta-pinene, beta-patchoulene, alpha-muurolene, alpha-pinene, alpha-calacorene, gamma-muurolene, alpha-thujene, alpha-cubebene, and terpinen-4-ol	Simonsen et al. (2009)
B. gaudichaudiana	Spathulenol	Florao et al. (2012)
B. Genistelloides	Palustrol and spathulenol	Florao et al. (2012)
B. grisebachii	Thymol, thymol methyl ether, thymyl acetate, alpha-pinene, alpha-humulene, and globulol	Hadad et al. (2007)
B. latifolia	Limonene, beta-phellandrene, sabinene, beta-pinene, and alpha-pinene	Valarezo et al. (2013)
B. magellanica	4-hydroxyacetophenone, massoia lactone, alpha-cadinol, gamma-eudesmol, elemol, beta-eudesmol, and caryophyllene oxide	Simonsen et al. (2009)
B. megapotamica	Spathulenol, and caryophyllene oxide	Budel et al. (2012)
B. Mesoneura	Limonene, alpha-thujene, alpha-pinene, sabinene, beta-pinene, myrcene, *p*-cymene, (E)-beta-ocimene, gamma-terpinene, spathulenol, and alpha-cadinol	Trombin-Souza et al. (2017)
B. microdonta	Caryophyllene oxide, elemol, spathulenol, beta-caryophyllene, and germacrene D	Lago et al. (2008) and Sayuri et al. (2010)
B. Milleflora	Viridiflorol, beta-caryophyllene, germacrene-D, Bicyclogermacrene, alpha-humulene, limonene, (E)-beta-ocimene, gamma-terpinene, spathulenol, and alpha-cadinol	Besten et al. (2014), Pereira et al. (2016), Pereira et al. (2017), and Trombin-Souza et al. (2017)
B. Myriocephala	Alpha-thujene, alpha-pinene, sabinene, beta-pinene, myrcene, *p*-cymene, limonene, (E)-beta-ocimene, gamma-terpinene, spathulenol, and alpha-cadinol	Trombin-Souza et al. (2017)
B. myrtilloides	Germacrene D	Zunino et al. (1998)
B. Notosergila	Alpha-pinene, limonene, beta -caryophyllene, and spathulenol	Cobos et al. (2001)
B. oblongifolia	Alpha-thujene, alpha-pinene, sabinene, beta-pinene, myrcene, *p*-cymene, limonene, (E)-beta-ocimene, gamma-terpinene, spathulenol, and alpha-cadinol	Trombin-Souza et al. (2017)
B. obtusifolia	Limonene, germacrene-D, alpha-pinene, beta-pinene, bicyclogermacrene, and delta-cadinene	Valarezo et al. (2015)
B. ochracea	Spathulenol, and caryophyllene oxide	Budel et al. (2012)
B. patens	Beta-caryophyllene, aromadendrene, bicyclogermacrene, spathulenol, caryophyllene oxide, linalool and beta-pinene	da Silva et al. (2018)

(continued)

Table 13.1 (continued)

Specie	Compounds	References
B. pentaptera	Sabinene, himachalol, beta-pinene, and delta-3-carene	Perera et al. (2017)
B. Psiadioides	Beta-pinene, delta-3-carene, limonene, and ocimene	Negreiros et al. (2016)
B. Regnelli	Bicyclogermacrene, delta-cadinene, and delta-car-3-ene	Lago et al. (2008)
B. rufescens	Limonene, and *trans*-nerolidol	Zunino et al. (1998)
B. salicifolia	Alpha-pinene, camphene, beta-pinene, alpha-phellandrene, alpha-cubebene, beta-Cariophyllene, 6,9-guaiadiene, germacrone, (Z)-beta-ocimene, germacrene D, beta-cubebene, alpha-thujene	Flores et al. (2009), and Sosa et al. (2012)
B. schultzii	Spathulenol, and limonene	Lago et al. (2008)
B. semiserrata	Spathulenol, caryophyllene oxide, viridiflorol, carotol, alpha-cadinol, alpha-pinene, beta-pinene, limonene, beta-caryophyllene, gamma-muurolene), bicyclogermacrene, and (E)-nerolidol	Besten et al. (2012) and Vannini et al. (2012)
B. spartioides	Alpha-phellandrene, sabinene, alpha-pinene, camphor, limonene, citronellal, carvone, spathulenol, and 6R-7R-bisabolone	van Baren et al. (2002), Oliva et al. (2007), and Barud et al. (2014)
B. tenella	Spathulenol	Biurrun et al. (2005)
B. tricuneata	(E)-nerolidol	Arze et al. (2004)
B. trimera	Alpha-humulene, limonene, alpha-thujene, alpha-pinene, sabinene, beta-pinene, myrcene, *p*-cymene, (E)-beta-ocimene, gamma-terpinene, spathulenol, and alpha-cadinol	Lago et al. (2008)
B. trinervis	Alpha-thujene, alpha-pinene, sabinene, beta-pinene, beta-phellandrene, (E)-Lachnophyllum acid methylester, (Z)-lachnophyllum acid methyl ester, caryophyllene oxide, viridiflorol, germacrene D, germacrene B, spathulenol, delta-3-carene, globulol, *cis*-muurola-4(14), 5-diene, bicyclogermacrene, ar-curcumene, sabinene	Albuquerque et al. (2004), Sobrinho et al. (2016), and Chaverri and Ciccio (2017)
B. uncinella	Alpha-pinene, limonene, beta-caryophyllene, spathulenol, caryophyllene oxide, viridiflorol, alpha-cadinol, (E)-nerolidol, globulol, (E)-nerolidol, bicyclogermacrene, and terpinen-4-ol	Frizzo et al. (2001), Fabiane et al. (2008), and Ascari et al. (2012)

The essential oil of *B. dracunculifolia* is the most studied among all others EOs obtained from this genus (Lage et al. 2015; Lago et al. 2008; Fabiane et al. 2008; Parreira et al. 2010; Florao et al. 2012; Besten et al. 2014; Salazar et al. 2018). This fact must be due to the close relationship between this species and propolis, a resinous material produced by bees (*Apis mellifera*) that is used as a sanitizer and hive-repairing component (Parreira et al. 2010; Lage et al. 2015; Campos et al. 2016). To produce propolis, bees collect plant buds and mix them with wax: *B.*

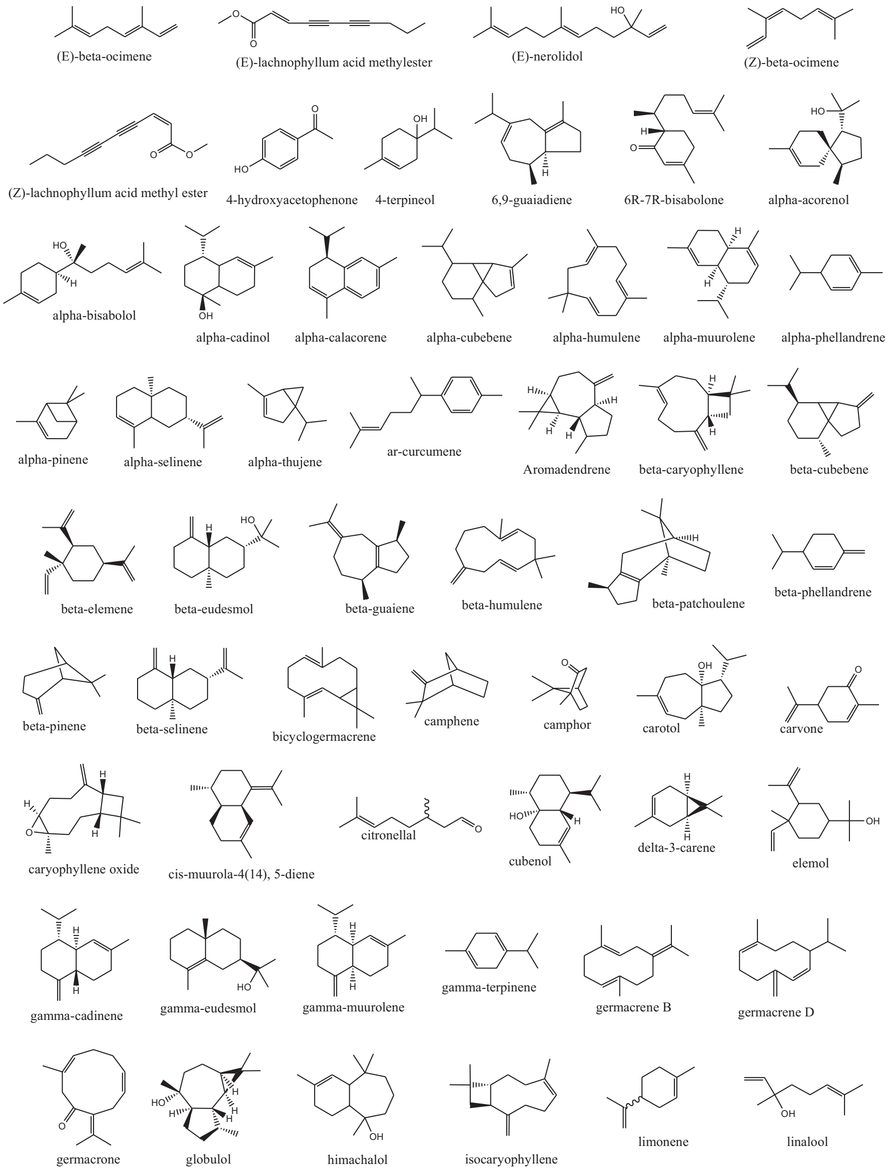


Fig. 13.3a Chemical structures of mono- and sesquiterpenes found in *Baccharis* essential oils. Source: NIST (National Institute of Standards and Technology) databank (Linstrom and Mallard 2018)

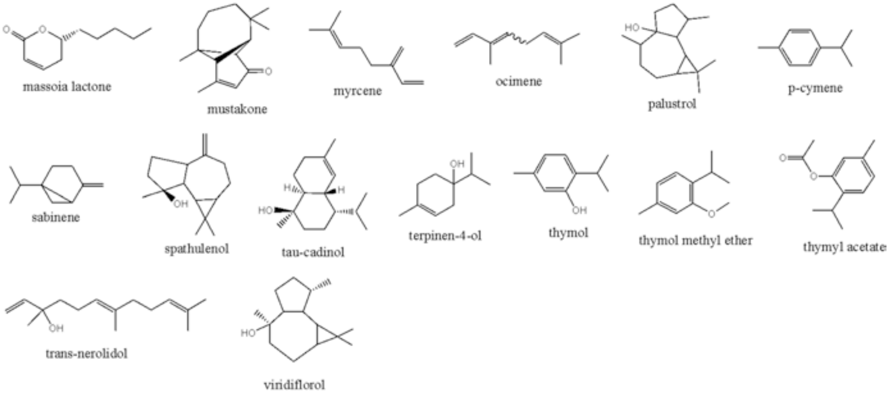


Fig. 13.3b Chemical structures of mono- and sesquiterpenes found in *Baccharis* essential oils. Source: NIST (National Institute of Standards and Technology) databank (Linstrom and Mallard 2018)

dracunculifolia is the main botanical source of Brazilian green propolis (BGP). In Brazil, BGP is the most studied and economically relevant tropical propolis, which is typically found in the South Eastern Region, where *B. dracunculifolia* popularly called “alecrim do campo” occurs (Parreira et al. 2010; Figueiredo-Rinhel et al. 2013; Lage et al. 2015; Campos et al. 2016). In fact, sesquiterpenes that are found in *B. dracunculifolia* like (E)-nerolidol, beta-caryophyllene, spathulenol, and γ-cadinene are also present in BGP and are responsible for the similar and peculiar aroma of both “alecrim do campo” EO and BGP. Moreover, such compounds are associated with several biological effects, including antimicrobial activity, among others. Especially in Asian markets, BGP prices can reach more than U$ 100 per kg and BGP extracts are incorporated in several “natural medicines,” cosmetics, toiletries, food, and beverages, as well as in food supplements (Marostica et al. 2008; Figueiredo-Rinhel et al. 2013).

Although other *Baccharis* EOs are not associated with economically relevant products like propolis, studies of these EOs are significant from the ecological and academic points of view, since they possess a different biological potential and present geographical and seasonal variations (see references in Table 13.1). Spathulenol, limonene, beta-pinene, alpha-pinene, sabinene, beta-caryophyllene, alpha-cadinol, caryophyllene oxide, germacrene D, bicyclogermacrene, and alpha-thujene are, among others, the most frequently found terpenoids in these others *Baccharis* Eos (Table 13.1).

3 *Baccharis* Diterpenes

Diterpenes are a broad and diversified class of secondary metabolites, widely distributed among different organisms, mainly in plants and fungi, originated from the head-tail coupling of four C5 isoprene units (Figueiredo-Rinhel et al. 2013). This class of natural products presents a great structural variety, since the GGPP units (Fig. 13.1) can rearrange in many different manners. Several skeleton types and distinct chemical functionalization have been reported for diterpenoids, which are classified according to the number and cyclization patterns of their chemical skeletons (Garcia et al. 2007; de Sousa et al. 2018). Acyclic-, bicyclic-, tricyclic-, tetracyclic-, and macrocyclic-type diterpenes (Fig. 13.4) have been isolated and identified from a diverse number of natural sources (De Sousa et al. 2018).

Phytochemical studies have been performed with aerial parts, leaves, stems, flowers, and exudates from *Baccharis* species during the two last decades. Phenolic and terpenoid compounds are described as the main metabolites found in these

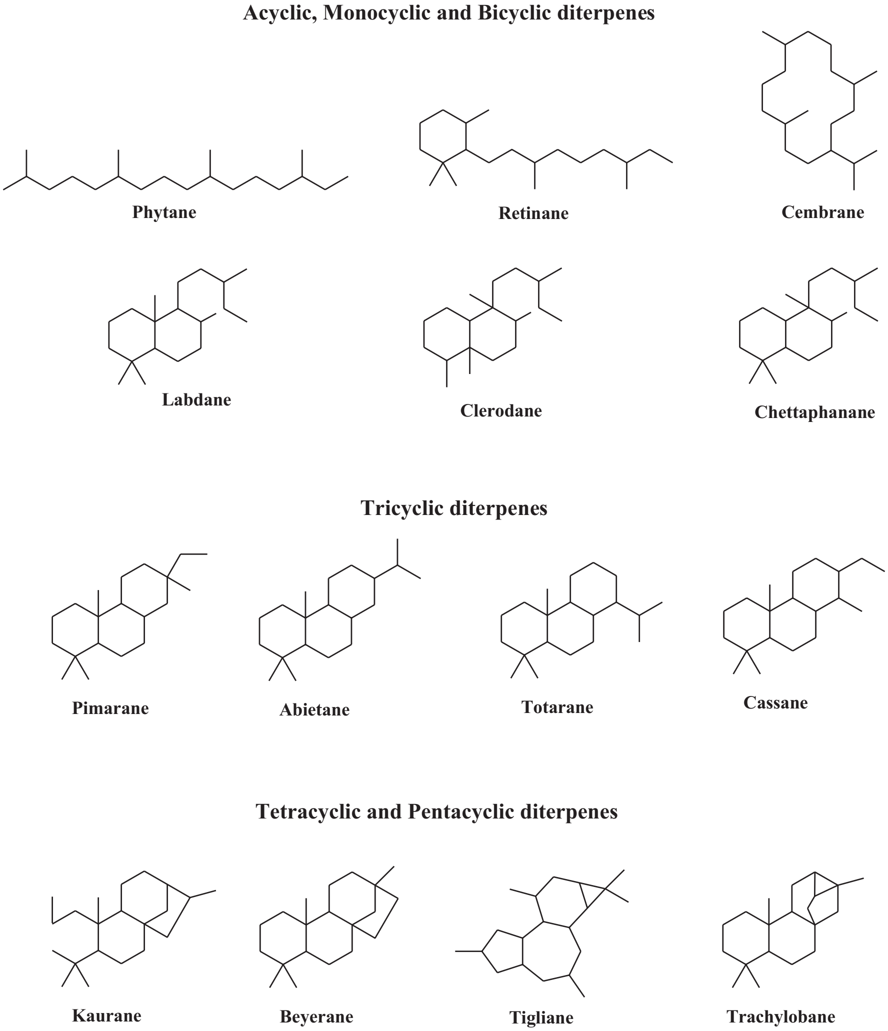
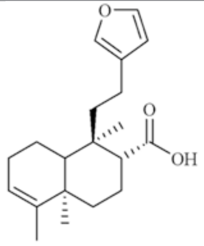
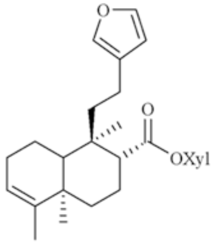
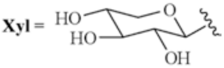
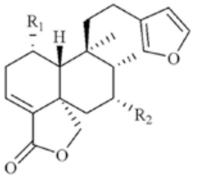
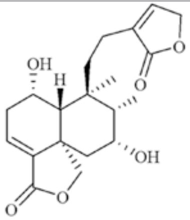
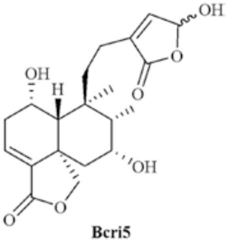
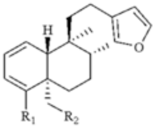
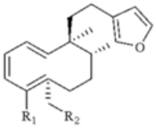
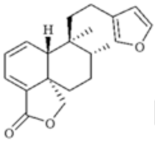
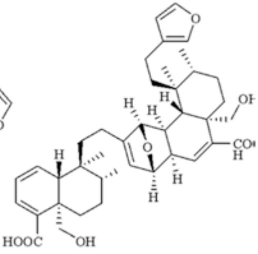
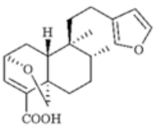
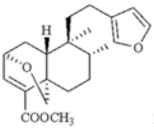
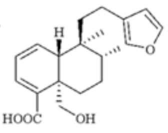
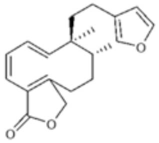
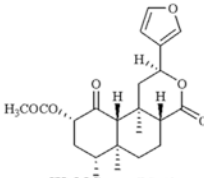


Fig. 13.4 Some examples of skeleton types of diterpenes related to their number of rings

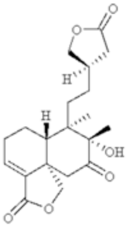
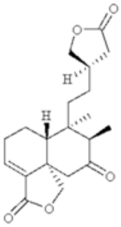
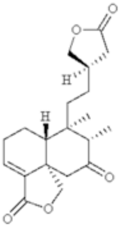
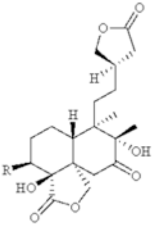
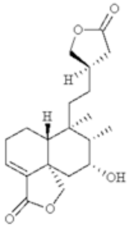
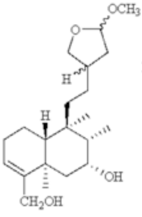
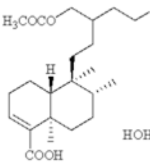
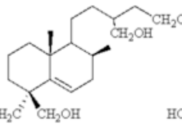
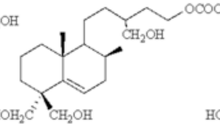
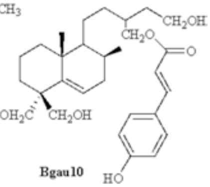
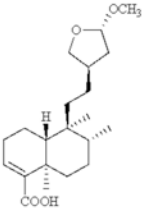
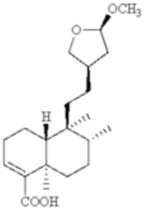
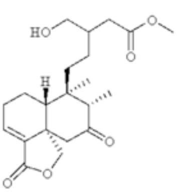
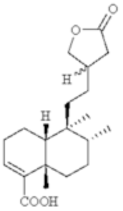
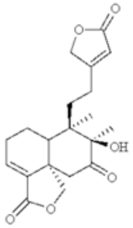
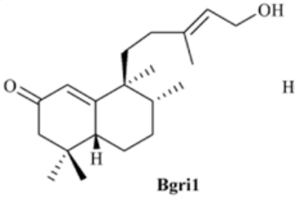
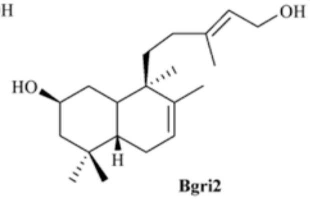
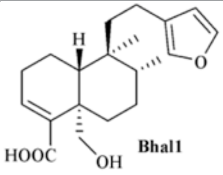
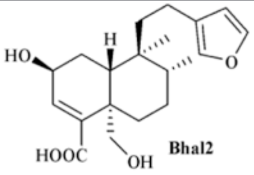
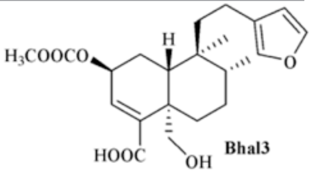
botanical sources, in which the presence of flavonoids and diterpenes is noteworthy (Campos et al. 2016). Regarding diterpenes, the scientific literature pointed out the biosynthesis of three main carbon skeletons in *Baccharis* species – kaurane, labdane, and neo-clerodane type-diterpenes. Many diterpenes were isolated or identified from *Baccharis* species until 2018 (Table 13.2).

Table 13.2 Examples of diterpenes obtained through chemical studies from *Baccharis* species

Species, references, and structures
B. boliviensis (Campos et al. 2016)
 **Bbol1**  **Bbol2** 
B. crispa (Cenal et al. 1997)
 **Bcri1** - R1 = R2 = OH **Bcri2** - R1 = H; R2 = OH **Bcri3** - R1 = R2 = H  **Bcri4**  **Bcri5**
B. flabellata (Hikawczuk et al. 2006; Funes et al. (2018a, b)
 **Bfla1** - R1 = COOH; R2 = OCOCH3  **Bfla2** - R1 = COOH; R2 = OCOCH3  **Bfla4**  **Bfla5**  **Bfla6**  **Bfla7**  **Bfla8**  **Bfla9**  **Bfla10**
B. gaudichaudiana [3, 60–63]

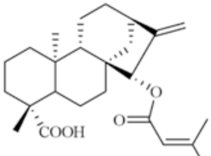
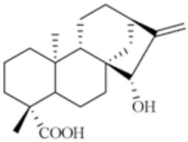
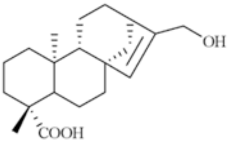
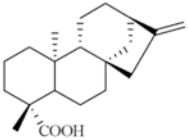
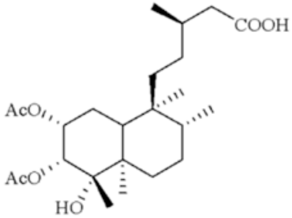
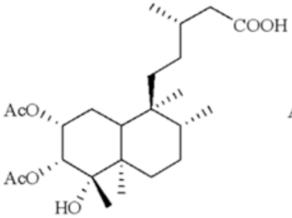
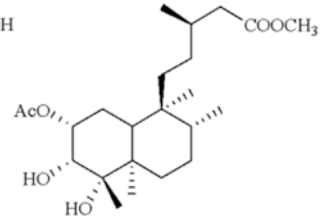
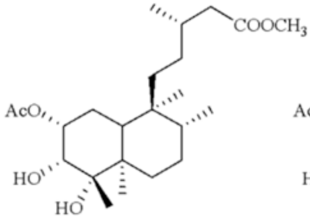
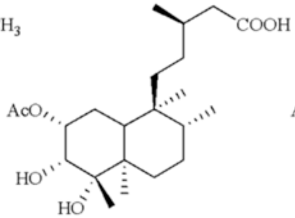
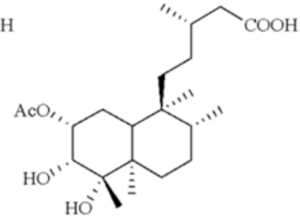
(continued)

Table 13.2 (continued)

Species, references, and structures
 **Bgau1**  **Bgau2**  **Bgau3**  **Bgau4** - R = *p*-bromobenzoyl  **Bgau5**
 **Bgau6**  **Bgau7**  **Bgau8**  **Bgau9**  **Bgau10**
 **Bgau11**  **Bgau12**  **Bgau13**  **Bgau14**  **Bgau15**
B. grisebachii (Feresin et al. 2003)
 **Bgri1**  **Bgri2**
B. halimifolia (Jakupovic et al. 1990)
 **Bhal1**  **Bhal2**  **Bhal3**
B. illinita (Campos et al. 2016; Verdi et al. 2004)

(continued)

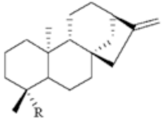
Table 13.2 (continued)

Species, references, and structures
 **Biln1**  **Biln2**  **Biln3**  **Biln4**
B. marginalis (Campos et al. 2016; San-Martin et al. 2010)
 **Bmar1**  **Bmar2**  **Bmar3**  **Bmar4**  **Bmar5**  **Bmar6**
B. minutiflora (Bohlmann et al. 1982)

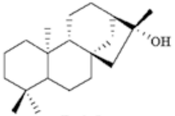
(continued)

Table 13.2 (continued)

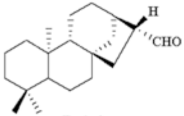
Species, references, and structures



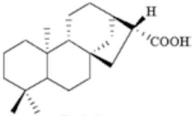
Bmin1 - R = CH_3
Bmin2 - R = CHO
Bmin3 - R = COOH
Bmin4 - R = CH_2OH



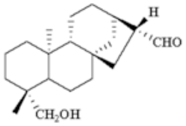
Bmin5



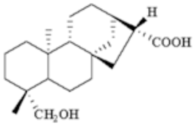
Bmin6



Bmin7



Bmin8



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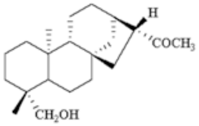

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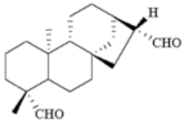
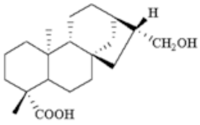
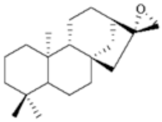


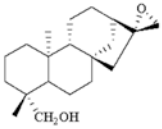
Bmin11



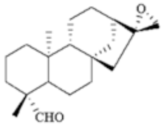
Bmin12



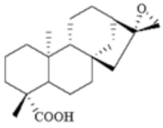
Bmin13



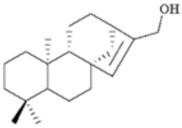
Bmin14



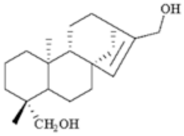
Bmin15



Bmin16

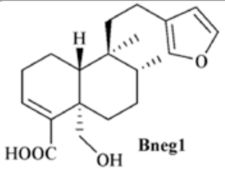


Bmin17

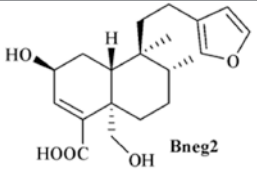


Bmin18

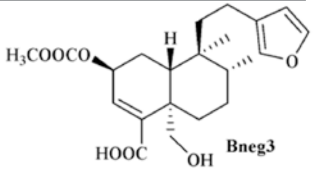
B. neglecta (Jakupovic et al. 1990)



Bneg1

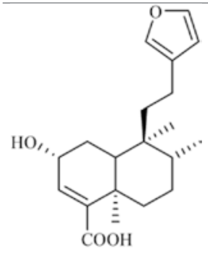


Bneg2



Bneg3

B. patens (Campos et al. 2016)

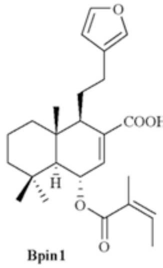
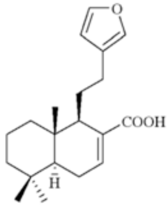
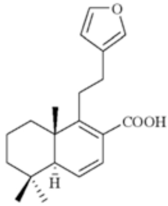
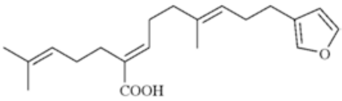
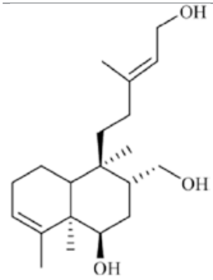
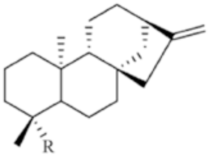
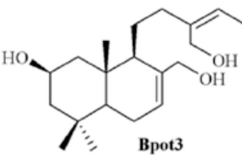
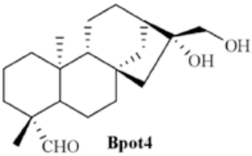
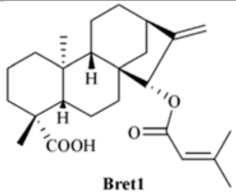
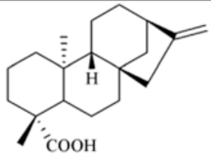
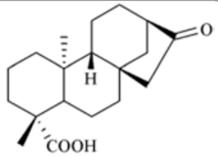


Bpat1

B. pingraea (Wachter et al. 1999)

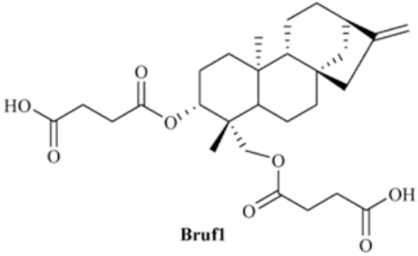
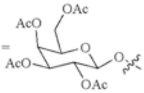
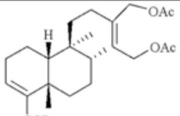
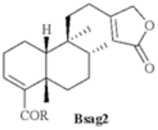
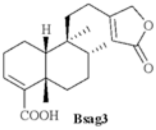
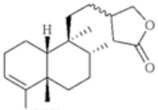
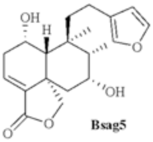
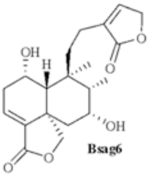
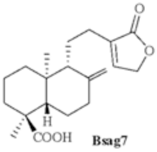
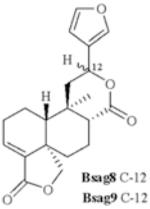
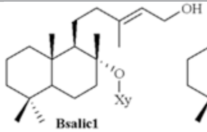
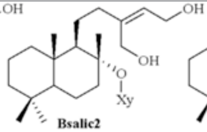
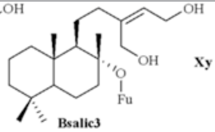
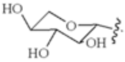
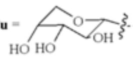
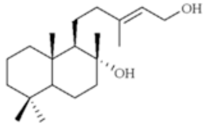
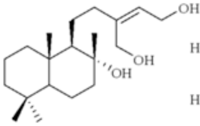
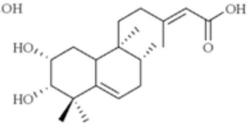
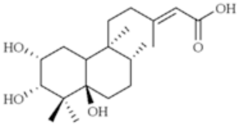
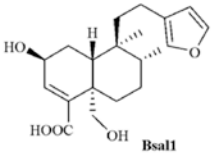
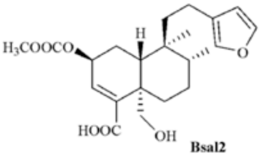
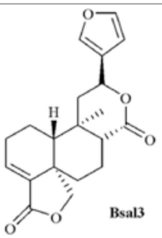
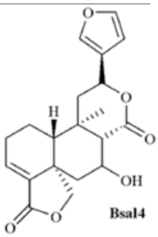
(continued)

Table 13.2 (continued)

Species, references, and structures
B. pingraea (Wachter et al. 1999)
 **Bpin1**  **Bpin2**  **Bpin3**  **Bpin4**
B. platypoda (Campos et al. 2016)
 **Bpla1**
B. potosina (Jakupovic et al. 1990)
 **Bpot1** - R = CHO **Bpot2** - R = COOH  **Bpot3**  **Bpot4**
B. retusa (Ueno et al. 2018a, b)
 **Bret1**  **Bret2**  **Bret3**
B. rufescens (Campos et al. 2016)

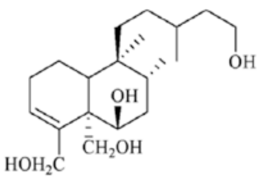
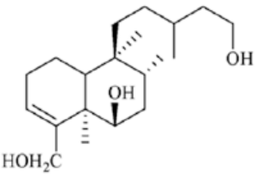
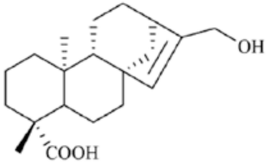
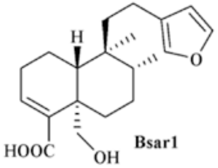
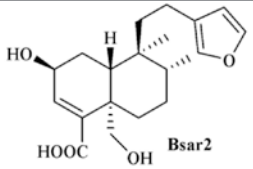
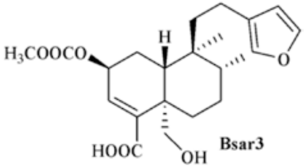
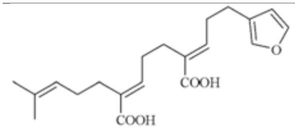
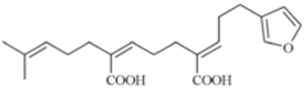
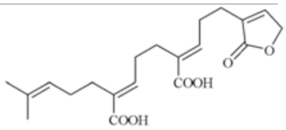
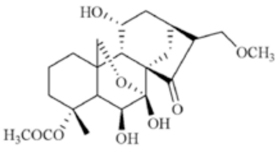
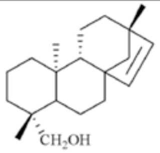
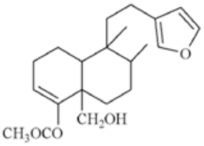
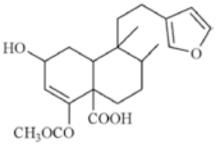
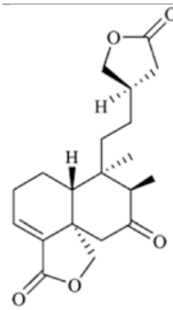
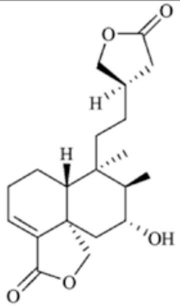
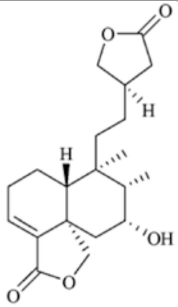
(continued)

Table 13.2 (continued)

Species, references, and structures
 **Brufl**
B. sagittalis (Campos et al. 2016)
Bsag1/Bsag2 - R =   **Bsag1**  **Bsag2**  **Bsag3**  **Bsag4**  **Bsag5**  **Bsag6**  **Bsag7**  **Bsag8** C-12 (*R*) **Bsag9** C-12 (*S*)
B. salicifolia (Campos et al. 2016; Jakupovic et al. 1990)
 **Bsalic1**  **Bsalic2**  **Bsalic3** **Xy** =  **Fu** =   **Bsalic4**  **Bsalic5**  **Bsalic6**  **Bsalic7**
B. salicina (Jakupovic et al. 1990)
 **Bsal1**  **Bsal2**  **Bsal3**  **Bsal4**

(continued)

Table 13.2 (continued)

Species, references, and structures
B. salzmannii (Campos et al. 2016)
 **Bsalz1**  **Bsalz2**  **Bsalz3**
B. sarathroides (Jakupovic et al. 1990)
 **Bsar1**  **Bsar2**  **Bsar3**
B. thymifolia (Hikawczuk et al. 2008)
 **Bthy1**  **Bthy2**  **Bthy3**
B. tola (Simirgiotis et al. 2016)
 **Btog1**  **Btog2**  **Btog3**  **Btog4**
B. trimera (Januario et al. 2004; Garcia et al. 2014; Campos et al. 2016)
 **Btri1**  **Btri2**  **Btri3**

Several diterpenes have been considered as the active compounds of various medicinal plants, due to their wide spectrum of pharmacological effects (de Sousa et al. 2018; Liu et al. 2018). In fact, scientific reports point out that this class of natural products possesses remarkable biological properties such as antiparasitic (Ambrosio et al. 2008), antihypertensive (Ambrosio et al. 2004; Tirapelli et al. 2010), anti-inflammatory and analgesic (Mizokami et al. 2012; Possebon et al. 2014), cytotoxicity against tumor cell lines (Batista et al. 2013; da Costa et al. 2018), and antimicrobial (Leandro et al. 2014; Severiano et al. 2010), among others (Kato et al. 2012; Xu et al. 2018; Liu et al. 2018).

Regarding the *Baccharis* diterpenes, several authors have investigated and reported their biological activities (Table 13.3).

From all biological properties that have been reported, the feeding-deterrent potential against insects displayed by neo-clerodane type-diterpenes from *Baccharis* species is highlighted in the literature (Hikawczuk et al. 2006; Cifuente et al. 2002; Hikawczuk et al. 2008; Sosa et al. 1994), and some efforts to understand the structure–activity relationships related with this class of compounds have been carried out (Hikawczuk et al. 2006; Cifuente et al. 2002).

Cifuente et al. (2002) evaluated the insect antifeedant activity of several clerodane-type diterpenes isolated from three *Baccharis* species (*B. sagittalis*, *B. crispa*, and *B. spicata*) against *Tenebrio molitor* larvae (Coleoptera: Tenebrionidae). The results obtained from this study allowed the authors to suggest that the presence of a β-substituted furan ring (A; Fig. 13.6) or a β-substituted butenolide group (B; Fig. 13.6) on the C-9 side chain plays an important role in the

Table 13.3 Relevant biological activities displayed by *Baccharis* diterpenes, reported in the last two decades

Biological activity	Active diterpenes	References
Insect antifeedant	Bsag3; Bsag5; Bsag8; Bthy1; Bthy3	Cifuente et al. (2002) and Hikawczuk et al. (2008)
Antimicrobial	Bgri2	Feresin et al. (2003)
Cytotoxicity against cancer cell lines	Bgau10	(Fullas et al. 1994)
ROS and RNS scavenging abilities	Bfla5; Bfla8	Funes et al. (2018a, b
Antinociceptive	Bfla5; Bfla8	Funes et al. (2018a, b)
Influx and mobilization of intracellular calcium	Btri1; Btri2	Garcia et al. (2014)
NGF (Nerve Growth Factor) potentiation	Bgau6; Bgau11; Bgau12; Bgau14	Guo et al. (2006) and Guo et al. (2007)
Antiproteolytic and antihemorrhagic	Btri3	Januario et al. (2004)
Relaxant effect on rat vascular smooth muscle	Btri3	Torres et al. (2000)
Antitrypanosomal	Bret1; Bret3	Ueno et al. (2018a, b)

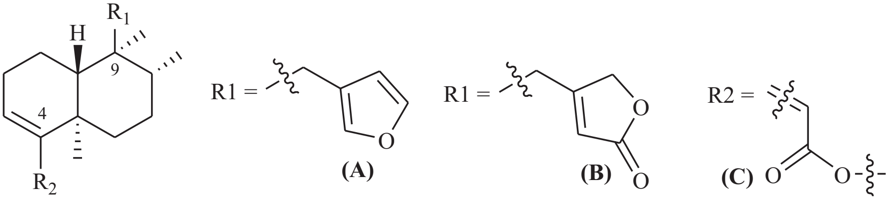


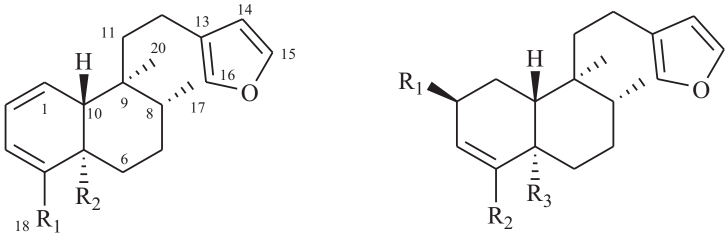
Fig. 13.5 Chemical groups presented in clerodane-type diterpenes related to their antifeedant activity (Cifuente et al. 2002; Enriz et al. 1994)

antifeedant bioactivity displayed by these diterpenes. Moreover, the literature also pointed out the presence of an α,β-unsaturated carbonyl system insert in the *trans*-decaline system at C-4 (C; Fig. 13.5) of clerodane diterpenes as a prerequisite to the antifeedant bioactivity (Enriz et al. 1994).

More recently, Hikawczuk et al. (2006) investigated the antifeedant activity of *neo*-clerodanes diterpenes from *Baccharis flabellata* against the grain stored insect *Tribolium castaneum*, and some considerations on the structure–activity relationship were also established by the authors. Among the nine diterpenes investigated in this study, compounds **6 and 8** (Fig. 13.6**)** were shown to be more effective against *T. castaneum*.

As previously described in the literature, the presence of a furan or a butenolide group at C-9 side chain and an α,β-unsaturated carbonyl system inserted in the *tran*s-decaline at C-4 (or a C-4 *spiro*-epoxide) are basic structural requirements related to the antifeedant activity of the clerodane-type diterpenes (Cifuente et al. 2002; Enriz et al. 1994). However, conformational and electronic factors were also revealed to be important in the antifeedant activity displayed by this class of diterpenes (Hikawczuk et al. 2006).

From a molecular model investigation performed by Hikawczuk et al. (2006), it was possible to establish a correlation of the antifeedant activity and the distance between the heteroatom located at the C-9 side chain and the olefinic carbon at C-3. According to the authors, the optimum interatomic distance between these two moieties ranged from 8.117 to 9.694 Å (Hikawczuk et al. 2006; Li et al. 2016). This study was carried out taking into account the potential of the double bond at C-3 to act as a nucleophilic acceptor of proteins in a Michael-type addition reaction, which can be related to the ability of diterpenes to inhibit the feeding of *T. castaneum* (Hikawczuk et al. 2006). Finally, the authors observed positive values of the electrostatic charge in the olefinic carbons at C-3 for the active diterpenes (Fig. 13.6, compounds **6** and **8**), whereas negative values were observed for all inactive compounds (Hikawczuk et al. 2006).



1 - R1 = COOH; R2 = CH_2OAc

2 - R1 = $COOCH_3$; R2 = CH_2OAc

3 - R1 = COOH; R2 = CH_2OH

4 - R1 = $COOCH_3$; R2 = CH_2OH

5 - R1 = CH_2OH; R2 = CH_2OH

6 - R1 = H; R2 = COOH; R3 = CH_2OH

7 - R1 = OAc; R2 = COOH; R3 = CH_2OH

8 - R1 = H; R2-R3 = $COOCH_2$

9 - R1 = OAc; R2-R3 = $COOCH_2$

Fig. 13.6 Chemical structures of clerodane-type diterpenes from *B. flabellata* investigated as antifeedant against *T. castaneum* (Hikawczuk et al. 2006)

4 Final Considerations

This chapter discussed in detail some chemical features and biological activities of the most representative terpenes found in *Baccharis* species (volatile terpenes and diterpenes). However, squalene-derived compounds, like steroids and triterpenes, are also found in this genus and can be associated with some biological activities, mainly antiparasitic (da Silva et al. 2009a, b; Passero et al. 2011), antinociceptive (Freitas et al. 2009), and anti-inflammatory (Boller et al. 2010).

Finally, it is important to mention the occurrence of a particular type of *Baccharis* trichothecenes, named baccharinoids. These compounds are associated with cattle poisoning in South America fed with *B. megapotamica* and also with several biological activities such as antiviral, anticancer, antimalarial, and antifungal (de Carvalho et al. 2016).

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