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Pilocarpus spp.: A survey of its chemical constituents and biological activities

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Pilocarpus *species have been exploited as the only source of the imidazole alkaloid pilocarpine (used in glaucoma treatment), since its isolation up to the present. Almost all* Pilocarpus *species are native from Brazil. Because of the medicinal importance of pilocarpine, several of them are in the path of extinction. Other secondary metabolites, such as coumarins, flavonoids and terpenes, were described for* Pilocarpus *species. In this review the secondary metabolites, other than pilocarpine, isolated from* Pilocarpus *species and their biological activities were compiled. Although the variety of structures and the importance of the biological activities described in literature for* Pilocarpus *species this is an unexploited field of research in Natural Products and Pharmacology.*

Uniterms
- Rutaceae
- *Pilocarpus* spp.
- Secundary metabolites
- Biological activities

INTRODUCTION

Pilocarpus Vahl is one of the 150 genus that compose the Rutaceae family and it was first known in Europe from the reports of the early scientific expeditions made to Brazil (Gabriel Soares de Souza, in 1570, Guilherme Piso, in 1637, and Georg Marcgrave, in 1638). Several *Pilocarpus* species are popularly known by the name of "jaborandi" which was derived from the tupi-Guarani language, *ya-mbor-endi* (the one who causes mouth-dripping) (Holmsted *et al.*, 1975). Several Rutaceae species are important due to their economical value as food, ornamental and medicinal uses. Some of the most common examples are listed in Table I.

TABLE I - Examples of the several uses of Rutaceae species

Species	Usage	References
Citrus spp.	Horticulture, volatile oils	Albuquerque, 1968
Pilocarpus spp.	Medicinal (pilocarpine)	Albuquerque, 1968
Zanthoxylum spp.	Carpentry	Corrêa, 1975
Euxilophora paraensis Huber	Carpentry	Loureiro, Silva, 1968
Esenbeckia febrifuga St. Hil.	Medicinal (febrifuge)	Albuquerque, 1968 Corrêa, 1969

The *Pilocarpus* genus was defined in 1797 with the descriptions of the species *P. racemosus*, however the position of the new taxon was not indicated (Skorupa, 1996). The initial conflicts in the systematic studies of the Rutaceae family imposed difficulties to classify this genus (Pirani, 1999; Albuquerque, 1985).

The most complete study about this genus was performed by Kaastra (1982) that kept the classification of *Pilocarpus* accordingly to Engler and recognized the genus *Raulinoa* Cowan as part of the subtribe Pilocarpineae (Scheme 1).

The *Pilocarpus* species are distributed in a large region of the American continent from Southern Central-America (Mexico) until the Southern part of the South-American continent (Argentina, Paraguay). There are 16 species described for this genus accordingly to Skorupa (1996). From these 13 can be found in Brazil, and 11 occur exclusively in the Brazilian territory (Table II).

These plants started to be studied concerning their pharmacological properties only in 1873, when it was confirmed that "jaborandi" was a potent stimulant of the secretory system, showing sialagogue, diuretic and diaphoretic activities (Corrêa, 1969). Since then, infusions of "jaborandi" leaves have been used for the treatment of fevers, stomatitis, bronchitis, gout, psoriasis, kidney diseases and several others illnesses (Holmsted *et al.*, 1975).

After the isolation of the imidazole alkaloid pilocarpine (Figure 1, compound **1**), in 1875 (Gerrard, 1875; Hardy, 1875), and its employment in ophthalmology (Weber, 1876), the "jaborandi" reached the status of one of the most important plants in the Brazilian flora (Pinheiro, 1997).

Besides alkaloids, a number of secondary metabolites have been reported in *Pilocarpus* species such as coumarins (Amaro-Luis *et al.*, 1990), flavonoids (Bertrand *et, al* 2001), hydrocarbons (Skorupa *et al.*, 1998; Negri *et al.*, 1998), triterpenes (Andrade Neto *et al.*, 1994) and volatile oils (Craveiro *et al.*, 1979).

The main goal of this review is to point out the importance of the *Pilocarpus* spp. as a source of secondary metabolites in Rutaceae with a potential pharmacological activity.

SECONDARY METABOLITES OF *PILOCARPUS* SPP.

Alkaloids

The "jaborandi" alkaloids are mainly of the imidazole group and it is thought that *L*-histidine is the biosynthetic precursor of the imidazole moiety (Battersby, Openshaw, 1953; Brochmann-Hanssen *et al.*, 1975; Cordell, 1981; Dewick, 2000).

Pilocarpine and other related alkaloids were isolated from several *Pilocarpus* species (Table III). Although the structural resemblance, only pilocarpine posses CNS activity, as a direct cholinergic which stimulates the parasympathetic system (bladder, tear ducts, sudoriferous and salivary glands). This alkaloid is the elected drug in the glaucoma treatment (Korolkovas, 1996) and the sialagogue property of pilocarpine has been exploited to treat the xerostomy (dry mouth) caused by the radio- or chemotherapy of throat cancer or those in the head area (Miller, 1993; Valdez *et al.*, 1993).

Others alkaloids derived from *L*-tryptophan were also isolated from *Pilocarpus* species. Some examples are *N,N*-dimethyl-5-methoxy-triptamine **(10)** and *N,N*-dimethyl-triptamine **(11)** (known as DMT) obtained from

Family	Subfamily	Tribe	Subtribe	Genus
Rutaceae	**Rutoideae**	**Galipeae**	**Pilocarpineae**	***Pilocarpus***
		(Cusparieae)		*Essenbeckia*
	Dictyolomatoideae	Zanthoxyleae		*Metrodorea*
	Spathelioideae	Ruteae		*Raulinoa*
	Toddalioideae	Boroneae		*Galipea* *
	Flindersioideae	Diosmeae		*Raputia* *
	Citroideae			*Neoraputia* *

* cited by PIRANI (1999)

SCHEME 1 - Systematic classification of *Pilocarpus* genus in Rutaceae.

TABLE II - Distribution of *Pilocarpus* species (Skorupa, 1996)

Species	Localization
Pilocarpus alatus C. J. Joseph ex Skorupa	Brazil (Pará and Mato Grosso)
Pilocarpus carajaensis Skorupa	Brazil (Pará)
Pilocarpus demerarae Sandwith	Guiana Inglesa
Pilocarpus giganteus Engler	Brazil (Bahia, Espírito Santo, Minas Gerais, Rio de Janeiro and São Paulo)
Pilocarpus grandiflorus Engler	Brazil (Alagoas, Bahia and Espírito Santo)
Pilocarpus jaborandi Holmes	Brazil (Ceará and Pernambuco)
Pilocarpus manuensis Skorupa	Peru (Manu National Park)
Pilocarpus microphyllus Stapf ex Wardleworth	Brazil (Maranhão, Mato Grosso, Pará and Piauí), Surinam
Pilocarpus pauciflorus St. Hilaire	Brazil (Paraná, Santa Catarina, Rio de Janeiro and São Paulo) (subSpecies *pauciflorus*) Brazil (Bahia) (subspecies *clavatus*) Brazil (subSpecies *organensis*)
Pilocarpus pennatifolius Lemmaire	Brazil (Bahia, Goiás, Mato Grosso and Mato Grosso do Sul, Minas Gerais, Paraná, Pernambuco, Rio Grande do Sul, Santa Catarina and São Paulo), Paraguay (Caazapá, Paraguarí), Argentina (Missiones)
Pilocarpus peruvianus (Macbride) Kaastra	Bolivia, Brazil (Acre, Rodônia e Mato Grosso) and Peru
Pilocarpus racemosus Vahl	Mexico, Antilles, Colombia, Venezuela and British Guyana (subspecies *racemosus*) Venezuela and Colombia (subspecies *goudotianus*) Costa Rica and El Salvador (subspecies *viridulus*)
Pilocarpus riedelianus Engler	Brazil (Alagoas, Bahia, Espírito Santo, Paraíba and Pernambuco)
Pilocarpus spicatus St. Hilaire	Brazil (Bahia, Espírito Santo, Rio de Janeiro and São Paulo) (subspecies *spicatus*) Brazil (Bahia) (subspecies *longeracemosus*) Brazil (Ceará, Paraíba and Pernambuco) (subspecies *aracatensis*)
Pilocarpus sulcatus Skorupa	Brazil (Bahia and Minas Gerais)
Pilocarpus trachyllophus Holmes	Brazil (Bahia, Ceará, Minas Gerais and Piauí)

P. organensis leaves; both have a CNS activity causing hallucinations (Balsam, Voigtländer, 1978).

Dictamine **(14)** a quinoline alkaloid obtained from *P. grandiflorus* posses a structural relationship with coumarins and, probably because of this resemblance, this substance exhibited a photosensitizing activity (Ashwood *et al.*, 1982).

Coumarins

Coumarins are secondary metabolites biosynthesized from *p*-coumaric acid (a phenylalanine derived). Besides the simple coumarins, like scopolentin **(28)**, in *Pilocarpus* species are also found pyrano- or furanocoumarins either with linear — xantyletin **(13)**, chalepin **(32)** and bergapten **(20)** — or with an angular structure — allo-xantoxilletol **(17)** and 3-methoxy-angelicin **(24)**. Some coumarins found in *Pilocarpus* species may also be *O*-prenylated — donatin **(18)**, imperatorin **(23)** — or *C*-prenylated — osthole **(30)**.

Although studies on the isolation of secondary products from *Pilocarpus* sp. have been performed for a long time, the isolation of coumarins has only been reported just over a decade ago from the leaves of *P. goudotianus* (Amaro-Luis *et al.*, 1990). The efficacy of the jaborandi infusions in the treatment of skin diseases such as psoriasis and vitiligo might be related with this class of natural products. Nowadays, several coumarins (particularly the 8-methoxy-psoralen **(21)**) have been used for skin repigmentation (Manderfeld *et al.*, 1997).

Some coumarins also showed good results as germination inhibitors (MACÍAS *et al.*, 1993), insecticide

TABLE III - Alkaloids derived from *Pilocarpus* species and some related biological activities

Alkaloid	Species	Activities	References
pilocarpine **(1)**	*P. jaborandi*	Sialagogue	Gerrard, 1875
	P. microphyllus	Diuretic	Hardy, 1875
	P. pennatifolius	Febrifuge	Jowett, 1900
	P. racemosus		Mester, 1973
	P. trachyllophus		Payo Hill *et al.*, 1995
	P. riedelianus		Andrade Neto *et al.*, 1996
			Guerreiro *et al.*, 2003
isopilocarpine **(2)**	*P. jaborandi*	-	Gerrard, 1875
	P. microphyllus		Hardy, 1875
	P. pennatifolius		Mester, 1973
pilocarpidine **(3)**	*P. jaborandi*	-	Jowett, 1900
isopilocarpidine **(4)**	*P. jaborandi*	-	Jowett, 1900
pilosine **(5)**	*P. jaborandi*	-	Pyman, 1912
	P. microphyllus		Voigtländer, Rosenberg, 1959
			Tedeschi *et al.*, 1973
isopilosine **(6)**	*P. jaborandi*	-	Voigtländer, Rosenberg, 1959
epiisopilosine **(7)**	*P. jaborandi*	-	Tedeschi *et al.*, 1973
epiisopiloturine **(8)**	*P. jaborandi*	-	Tedeschi *et al.*, 1973
13-nor-7(11)-dehidro-pilocarpine **(9)**	*P. trachyllophus*	-	Andrade Neto *et al.*, 1996
N,N-dimethyl-5-methoxy-triptamine **(10)**	*P. organensis*	Hallucinogen	Balsam, Voigtländer, 1978
			Riba *et al.*, 2002
N,N-dimethyl-triptamine **(11)**	*P. organensis*	Hallucinogen	Balsam, Voigtländer, 1978
			Riba *et al.*, 2002
plastydesmine **(12)**	*P. grandiflorus*	-	De Souza *et al.*, 2003
(1*H)*-4-methoxy-2-quinolone **(13)**	*P. grandiflorus*	-	De Souza *et al.*, 2003
dictamine **(14)**	*P. grandiflorus*	Antifungic	Asswood-Smith *et al.*, 1982
		Vasorelaxing	Yu *et al.*, 1992
		Photosensitizing	De Souza *et al.*, 2002
		Anticoagulant	Su *et al.*, 1998

(Calcagno *et al.*, 2002; Ngwedson *et al.*, 2003; Manderfeld *et al.*, 1997), antioxidant (Shaw *et al.*, 2003; Hoult, Paya, 1996), and against Chagas' disease (Pavão *et al.*, 2002; Mafezoli *et al.*, 2000). Synthetic coumarins derived from seselin **(35)** exhibit potential activity against HIV (Huang *et al.*, 1994).

The known coumarins isolated from *Pilocarpus* species and their respective structures are listed in Table IV and Figure 2.

Flavonoids

Flavonoids represent one of the most important groups of phenolic natural products and, like coumarins, they are also biosynthesized from *L*-phenylalanine. These metabolites are obtained from *Citrus* species (Rutaceae) from seeds, fruits, flowers and leaves (Middleton, 1984). Among others, the suggested activities of flavonoids are: analgesic (Thirugnanasambanthan *et al.*, 1990), sedative (Medina *et al.*, 1997; Marder & Paladini, 2002), anti-inflammatory (Pathak *et al.*, 1991).

The antioxidant activity of these substances is due to the ability of reducing free radical formation and to scavenge free radicals. Accordingly to Makersby (1997), the neurodegenerative Alzheimer's disease manifestation is related to the production of these species in the organism. In this sense, flavonoids can be considered as promising drugs in the treatment of this disease (Kim *et al.*, 2002).

Hesperidin **(46)** was isolated from *P. trachyllophus* (Bertrand *et al.*, 2001). This substance is currently isolated from other Rutaceae, such as *Citrus* and *Zanthoxylum*

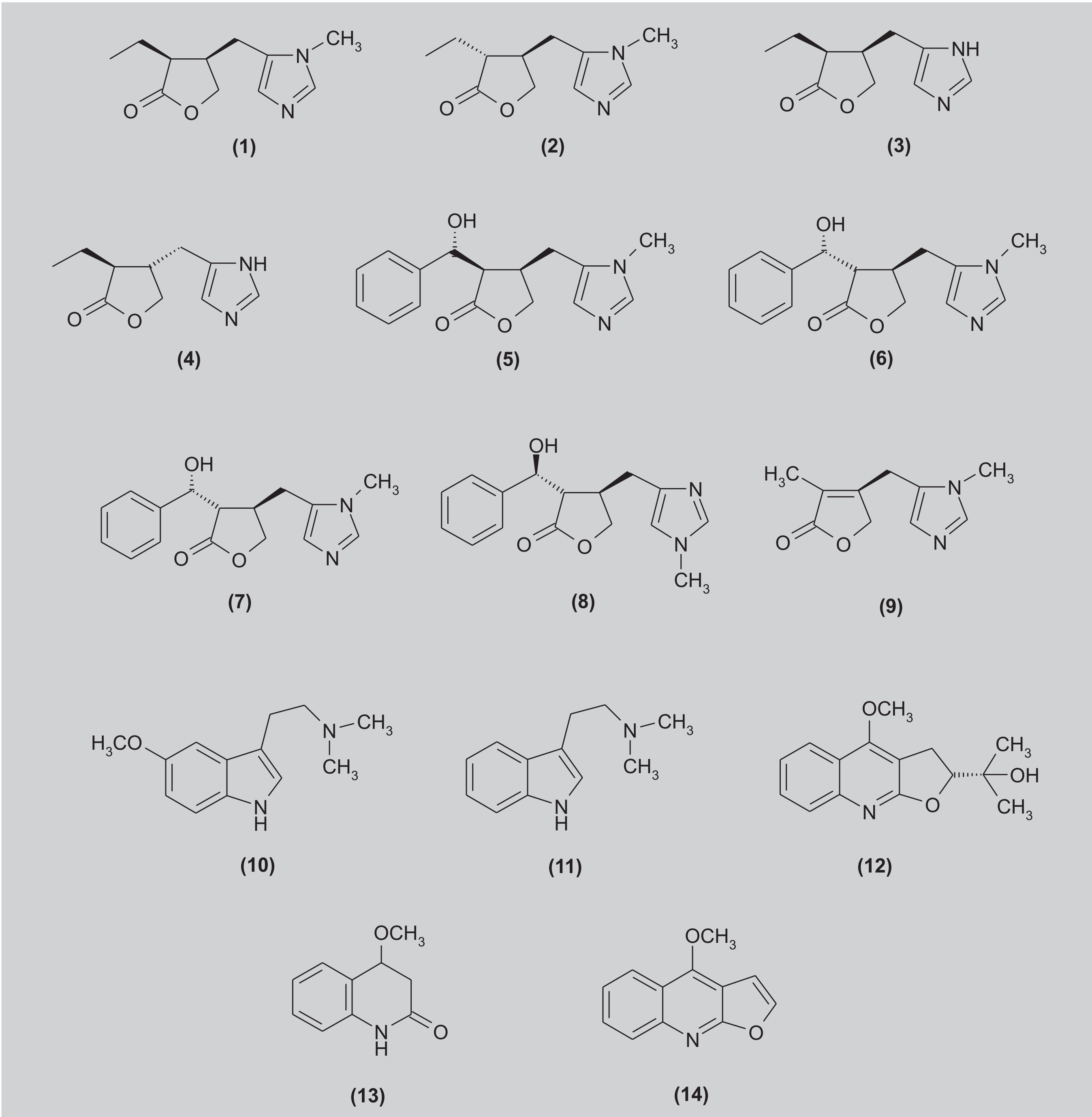


FIGURE 1 – Chemical structures of the alkaloids isolated from *Pilocarpus* species.

species (Kanes *et al.*, 1993; Horowitz, Gentili, 1963; Arthur *et al.*, 1956). This flavonoid has various pharmacological activities and some of them are anti-inflammatory, bactericidal, fungicidal, antiviral, abortive, analgesic and antipyretic (Garg *et al.*, 2001). Recently, hesperidin was obtained from *Valeriana* species ("the Valium of 19th century") and also exhibited sedative and sleep-enhancer properties (Marder *et al.*, 2003).

The following flavonoids, listed in Table V, were isolated from *P. trachyllophus* leaves.

Terpenes

Several reports dealt with the terpenes present in *Pilocarpus* species, mostly in volatile oils. Terpenes are biosynthesized from IPP (isopentenyl diphosphate),

TABLE IV - Coumarins isolated from *Pilocarpus* species and some related biological activities

Coumarin	Species	Activity	References
xantyletin **(15)**	*P. goudotianus*	Antifungic	Amaro-Luis *et al.*, 1990
	P. racemosus	Anti-PAF	Teng *et al.*, 1992
	P. riedelianus	Allelochemical	Macías *et al.*, 1993
		Insecticide	Calcagno *et al.*, 2002
xanthoxyletin **(16)**	*P. goudotianus*	Anti-PAF	Amaro-Luis *et al.*, 1990
		Allelochemical	Teng *et al.*, 1992
		Insecticide	Macías *et al.*, 1993
			Calcagno *et al.*, 2002
luvangetin **(17)**	*P. goudotianus*	Allelochemical	Amaro-Luis *et al.*, 1990
	P. racemosus	Insecticide	Compagnone, Rodriguez, 1993
			Macías *et al.*, 1993
			Calcagno *et al.*, 2002
donatin **(18)**	*P. goudotianus*	Allelochemical	Amaro-Luis *et al.*, 1990
		Insecticide	Macías *et al.*, 1993
			Calcagno *et al.*, 2002
allo-xanthoxilletol **(19)**	*P. goudotianus*	Allelochemical	Amaro-Luis *et al.*, 1990
		Insecticide	Macías *et al.*, 1993
			Calcagno *et al.*, 2002
bergapten **(20)**	*P. goudotianus*	Photosensitizing	Amaro-Luis *et al.*, 1990
	P. racemosus	Bactericide	Compagnone, Rodriguez, 1993
		Allelochemical	Macías *et al.*, 1993
		Insecticide	Manderfeld *et al.*, 1997
			Calcagno *et al.*, 2002
8-methoxy-psoralen **(21)**	*P. goudotianus*	Photosensitizing	Amaro-Luis *et al.*, 1990
	P. racemosus	Vasorelaxing	Compagnone, Rodriguez, 1993
		Bactericide	Macías *et al.*, 1993
		Allelochemical	Manderfeld *et al.*, 1997
		Insecticide	Chiou *et al.*, 2001
			Calcagno *et al.*, 2002
isopimpinellin **(22)**	*P. goudotianus*	Vasorelaxing	Amaro-Luis *et al.*, 1990
		Bactericide	Macías *et al.*, 1993
		Allelochemical	Chiou *et al.*, 2001
		Insecticide	Calcagno *et al.*, 2002
			Ngwendson *et al.*, 2003
imperatorin **(23)**	*P. goudotianus*	Vasorelaxing	Amaro-Luis *et al.*, 1990
		Allelochemical	Su *et al.*, 1998
		Insecticide	Chiou *et al.*, 2001
			Ngwendson *et al.*, 2003
tricocline **(24)**	*P. goudotianus*	-	Amaro-Luis *et al.*, 1990
(+)-elisin **(25)**	*P. goudotianus*	-	Amaro-Luis *et al.*, 1990
	P. grandiflorus		De Souza *et al.*, 2003
3,6-dimethoxy-angelicin **(26)**	*P. riedelianus*	-	Müller *et al.*, 1993
3-methoxy-angelicin **(27)**	*P. riedelianus*	-	Müller *et al.*, 1993
scopoletin **(28)**	*P. riedelianus*	Antioxidant	Müller *et al.*, 1993
	P. grandiflorus		De Souza *et al.*, 2002
			Shaw *et al.*, 2003
pimpinellin **(29)**	*P. riedelianus*	-	Müller *et al.*, 1993
osthole **(30)**	*P. riedelianus*	Anticoagulant	Müller *et al.*, 1993
		Vasorelaxing	Chiou *et al.*, 2001
meranzin hidrate **(31)**	*P. riedelianus*	-	Müller *et al.*, 1993
sphondin **(32)**	*P. riedelianus*	-	Müller *et al.*, 1993

TABLE IV - Coumarins isolated from *Pilocarpus* species and some related biological activities (continuation)

Coumarin	Species	Activity	References
auraptene **(33)**	*P. riedelianus*	Antitumoral	Müller *et al.*, 1993 Murakami *et al.*, 1997
chalepin **(34)**	*P. spicatus*	Anti-Chagas' disease	Pavão *et al.*, 2002
seselin **(35)**	*P. riedelianus*	Anti-HIV	Guerreiro *et al.*, 2001 Huang *et al.*, 1994
umbeliferone **(36)**	*P. riedelianus*	Antioxidant	Hoult, Paya, 1996 Guerreiro *et al.*, 2001
13,13-dimethyl-6 methoxy-2*H*, 8*H*-pyrano- (2,3)-cromen-2-one **(37)**	*P. riedelianus*	-	Guerreiro *et al.*, 2001
7-hydroxy-3-(1',1'-dimethyl-allyl)-8-methoxy-coumarin **(38)**	*P. riedelianus*	Bactericide Antifungic	Guerreiro *et al.*, 2001
3'-hydroxy-dipetalactone **(39)**	*P. grandiflorus*	-	De Souza *et al.*, 2001
3',4'-dihydro-3'-hydroxy-dipetalactone **(40)**	*P. grandiflorus*	Antifungic	De Souza *et al.*, 2003
3-(1',1'-dimethyl-allyl)-scopoletin **(41)**	*P. grandiflorus*	Antifungic	De Souza *et al.*, 2003

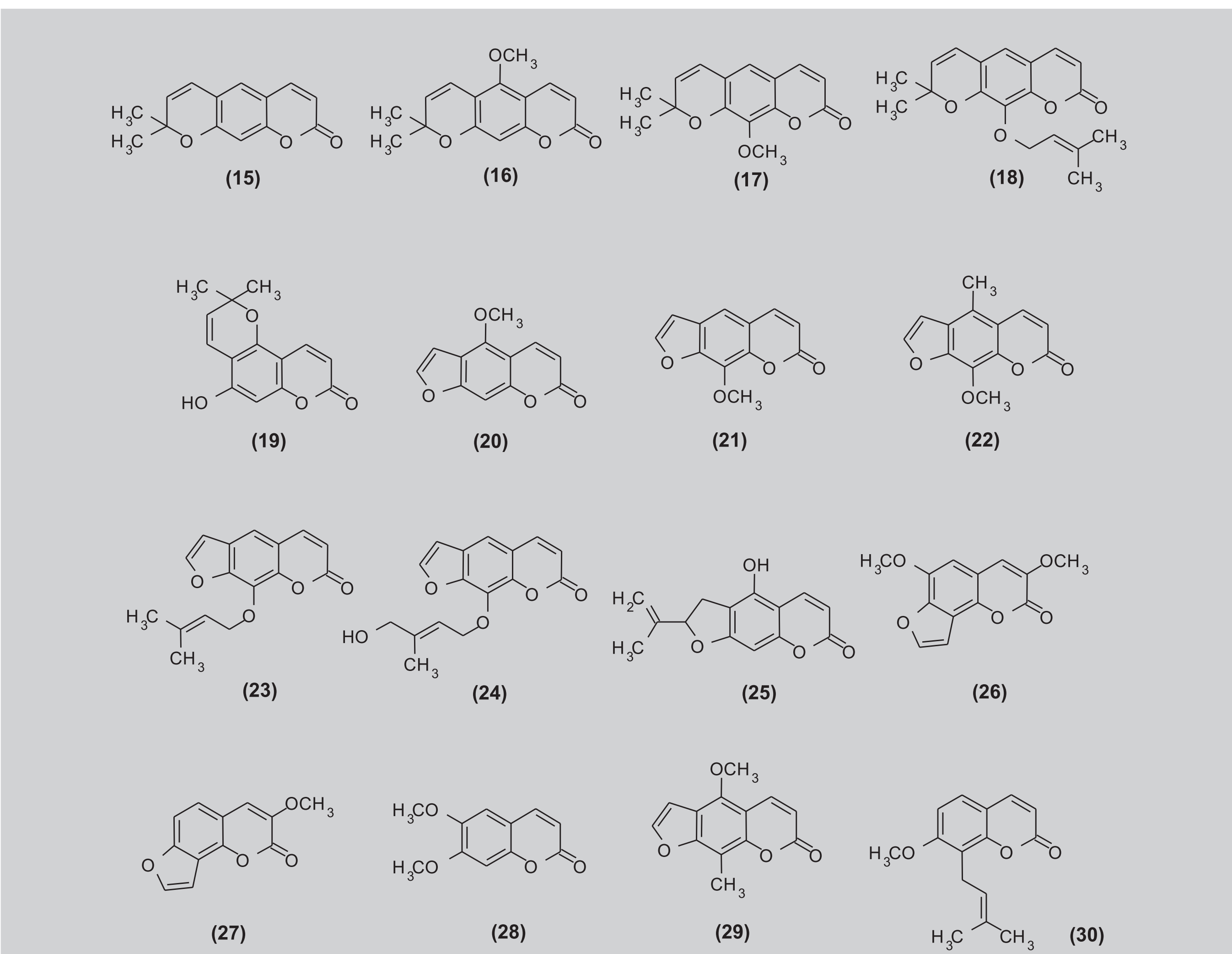


FIGURE 2 - Chemical structures of some coumarins isolated from de *Pilocarpus* species.

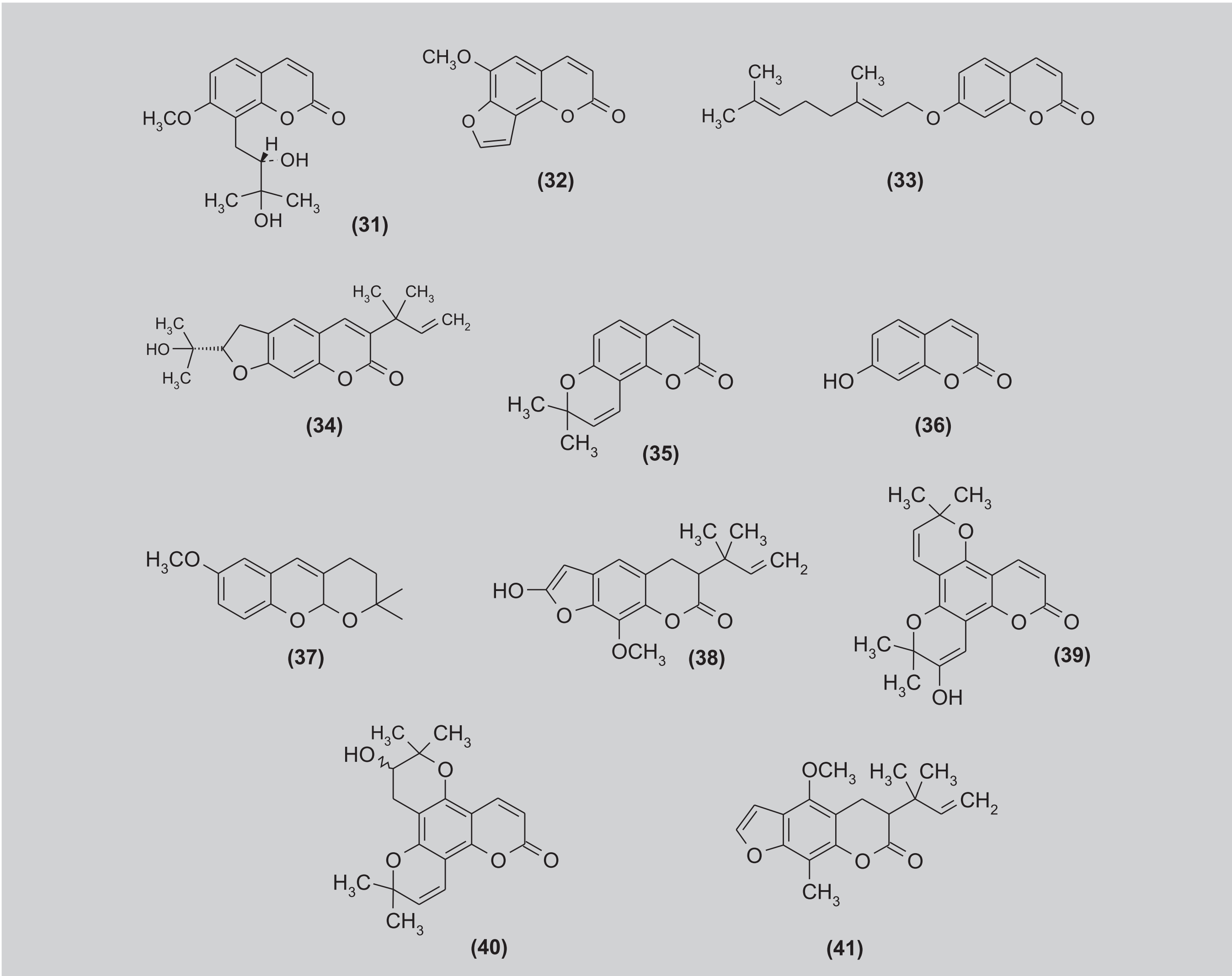


FIGURE 2 – Chemical structures of some coumarins isolated from de *Pilocarpus* species (continuation).

TABLE V - Flavonoids isolated from *Pilocarpus* species and some related biological activities

Flavonoid	Species	Activity	References
3,4',5,7-tetrahydroxy-3',6-dimethoxy-flavone-3-*O*-β-rutinoside **(42)**	*P. trachyllophus*		Bertrand *et al.*, 2001
3,4',5,7-tetrahydroxy-6-methoxy-flavone-3-*O*-β-rutinoside **(43)**	*P. trachyllophus*		Bertrand *et al.*, 2001
patulentine-3-*O*-β-rutinoside **(44)**	*P. trachyllophus*	Antioxidant (aglicone)	Bertrand *et al.*, 2001
axilarin **(45)**	*P. trachyllophus*	Antioxidant	Bertrand *et al.*, 2001 Kim *et al.*, 2002
hesperidin **(46)**	*P. trachyllophus*	Antioxidant Sedative	Andrade Neto *et al.*, 1996 Kim *et al.*, 2002

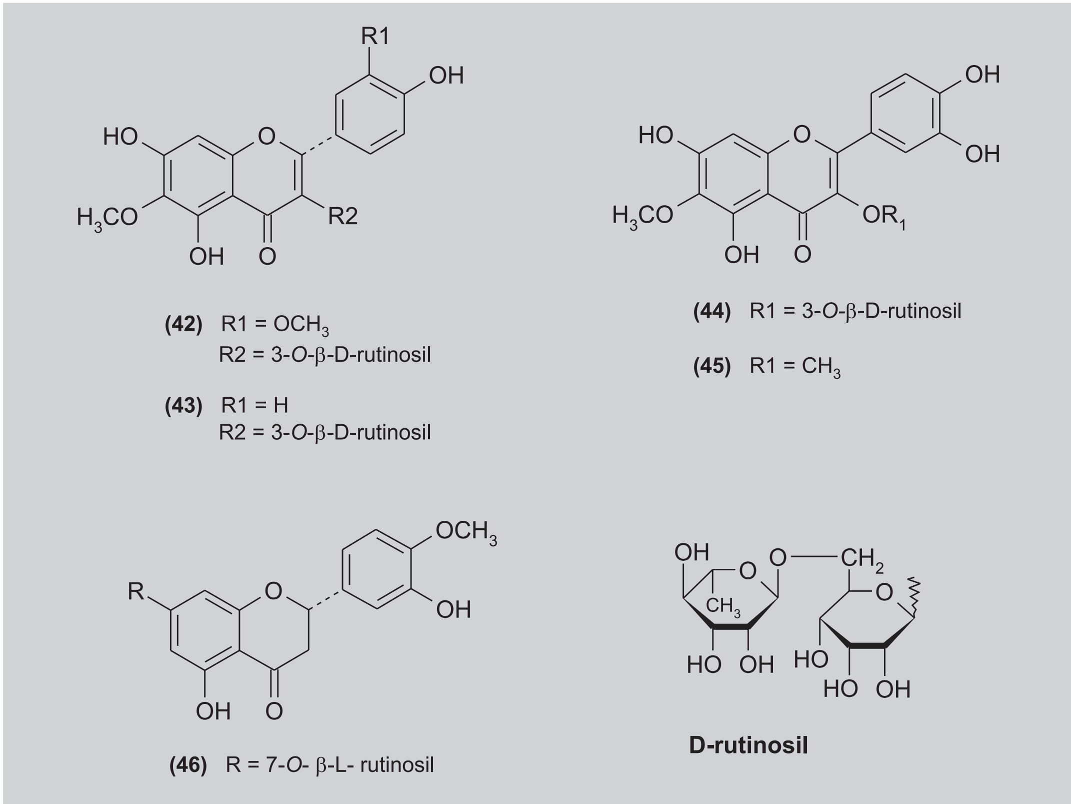


FIGURE 3 - Chemical structures of flavonoids isolated from *Pilocarpus* species.

through the mevalonate pathway that gives rise to the mono- (C10), sesqui- (C15), di- (C20) and triterpenes (C30).

There are many references about the importance of terpenes in plant metabolism, mainly as essential oils. Although it is of general sense that terpenes represent a fundamental tool in pollinator's attraction, guaranteeing a species reproduction. They also displayed a variety of biologic activities such as insecticide, antimicrobial and antiseptic (Figueiredo, 1992). The essential oils of *P. spicatus*, *P. gradiflorus* and *P. pauciflorus* species exhibited bactericidal activity against *Bacilus subtilis*, *Salmonella typhimurium*, *Escherichia coli* and *Pseudomonas aeruginosa* (Santos *et al.*, 1997).

Although the occurrence of triterpenes and steroids in plants is quite common, and these compounds were only reported in three *Pilocarpus* species (Table VI and Figure 4). For *P. grandiflorus* the triterpenes b-amyrin **(109)**, occotilone **(111)** and germanicol **(114)** were described. The b-amyrin acetate **(110)** obtained from *P. trachyllophus* showed a high cytostatic activity against cells of HEp-2 (Gomez *et al.,* 1997).

Additional pharmacological activities, such as angiogenic, antihelminthic, antimicrobial and antitumoral, were described only for the steroid β-sitosterol **(86)** (Moon *et al.*, 1999; Villasenor *et al.*, 2002; Singh, Singh, 2003; Awad *et al.*, 2003).

Other secondary metabolites isolated fom *Pilocarpus* species

Besides alkaloids, coumarins, flavonoids and terpenes there are minor compounds that can occur in some *Pilocarpus* species. Among these compounds are lignans, hydrocarbons and its alcohols, amides, carboxilic acids, esters and ketones derivatives (Table VII and Figure 5).

Lignans (also *L*-phenylalanine derivatives) were obtained from two different *Pilocarpus* species (Table VII). Lignans play an important role in the plant sustentation as cell wall constituents. The lignan lirioresinol B **(124)**, isolated from *P. grandiflorus* (De Souza *et al.*, 2003), showed antichagasic activity (Sauvain *et al.*, 1996).

The amide pellitorine **(125)** was found in *P. trachyllophus* (Andrade Neto *et al.*, 1995). This substance is frequently isolated from *Piper* species and it is widely known as an insecticide (He *et al.*, 2002).

TABLE VI - Terpenoids isolated from *Pilocarpus* species

Terpene (class)	Species	References
Monoterpenes		
3,7.7-trimethylbicyclo[3.1.1]-2-heptene **(47)**	*P. microphyllus*, *P. affinis*	Craveiro *et al.*, 1979
α-pinene **(48)**	*P. jaborandi*, *P. microphyllus*, *P. affinis*, *P. spicatus*, *P. grandiflorus*	Craveiro *et al.*, 1979 Santos *et al.*, 1997 Andrade Neto *et al.*, 2002
β-pinene **(49)**	*P. spicatus*, *P. grandiflorus*	Santos *et al.*, 1997 Andrade Neto *et al.*, 2002
canfene **(50)**	*P. spicatus*	Andrade Neto *et al.*, 2002
borneol **(51)**	*P. spicatus*	Andrade Neto *et al.*, 2002
linalool **(52)**	*P. spicatus*, *P. grandiflorus*	Santos *et al.*, 1997 Andrade Neto *et al.*, 2002
mircene **(53)**	*P. jaborandi*, *P. affinis*, *P. spicatus*, *P. grandiflorus*	Craveiro *et al.*, 1979 Santos *et al.*, 1997 Andrade Neto *et al.*, 2002
E-β-ocimene **(54)**	*P. spicatus, P. pennatifolius*	Andrade Neto *et al.*, 2002 Santos *et al.*, 2004
Z-β-ocimene **(55)**	*P. pennatifolius*	Santos *et al.*, 2004
Limonene **(56)**	*P. jaborandi*, *microphyllus*, *P. affinis*, *P. trachyllophus*, *P. spicatus*, *P. grandiflorus*	Craveiro *et al.*, 1979 Andrade Neto *et al.*, 1995 Santos *et al.*, 1997 Andrade Neto *et al.*, 2000, 2002
Sabinene **(57)**	*P. spicatus*	Andrade Neto *et al.*, 2002
δ-3-carene **(58)**	*P. spicatus*	Andrade Neto *et al.*, 2002
α-terpinene **(59)**	*P. spicatus*	Andrade Neto *et al.*, 2002
γ-terpinene **(60)**	*P. spicatus*	Andrade Neto *et al.*, 2002
α-terpineol **(61)**	*P. spicatus*	Andrade Neto *et al.*, 2002
terpinen-4-ol **(62)**	*P. spicatus*	Andrade Neto *et al.*, 2002
p-cimene **(63)**	*P. spicatus*	Andrade Neto *et al.*, 2002
β-felandrene **(64)**	*P. spicatus*	Andrade Neto *et al.*, 2002
1,8-cineole **(65)**	*P. spicatus*	Andrade Neto *et al.*, 2002
Sesquiterpenes		
Z,Z-farnesol **(66)**	*P. spicatus*	Andrade Neto *et al.*, 2002
E-nerolidol **(67)**	*P. spicatus*	Andrade Neto *et al.*, 2002
β-bisabolene **(68)**	*P. trachyllophus*, *P. spicatus*	Andrade Neto *et al.*, 1995 Santos *et al.*, 1997 Andrade Neto *et al.*, 2000, 2002
δ-cadinene **(69)**	*P. microphyllus*, *P. trachyllophus*, *P. spicatus*. *P. pennatifolius*	Craveiro *et al.*, 1979 Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2000, 2002 Santos *et al.*, 2004
γ-cadinene **(70)**	*P. trachyllophus*, *P. spicatus*	Andrade Neto *et al.*, 1995 Santos *et al.*, 1997 Andrade Neto e*t al.*, 2000, 2002
germacrene D **(71)**	*P. trachyllophus*, *P. spicatus*	Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2002

TABLE VI - Terpenoids isolated from *Pilocarpus* species (continuation)

Terpene (class)	**Species**	**References**
Sesquiterpenes		
β-cubebene **(72)**	*P. spicatus*, *P. pennatifolius*	Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2002 Santos *et al.*, 2004
γ-muurolene **(73)**	*P. spicatus*, *P. pennatifolius*	Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2002 Santos *et al.*, 2004
α-muurolene **(74)**	*P. spicatus*	Andrade Neto *et al.*, 2002
germacrene-4-D-ol **(75)**	*P. spicatus*	Andrade Neto *et al.*, 2002
α-cadinol **(76)**	*P. spicatus*	Andrade Neto *et al.*, 2002
cubenol **(77)**	*P. spicatus*	Andrade Neto *et al.*, 2002
T-muurolol **(78)**	*P. spicatus*	Andrade Neto *et al.*, 2002
calacorene **(79)**	*P. riedelianus*	Guerreiro *et al.*, 2001
α-calacorene **(80)**	*P. riedelianus*	Guerreiro *eta.*, 2001
γ-calacorene **(81)**	*P. riedelianus*	Guerreiro *et al.*, 2001
cadalene **(82)**	*P. riedelianus*	Guerreiro *et al.*, 2001
sesquichamaenol **(83)**	*P. riedelianus*	Guerreiro *et al.*, 2001
sesquichamaenol A **(84)**	*P. riedelianus*	Guerreiro *et al.*, 2001
δ-elemene **(85)**	*P. spicatus*	Andrade Neto *et al.*, 2002
germacrene A **(86)**	*P. spicatus*	Andrade Neto *et al.*, 2002
germacrene B **(87)**	*P. pennatifolius*	Santos *et al.*, 2004
selinene **(88)**	*P. affinis*, *P. pennatifolius*	Craveiro *et al.*, 1979 Santos *et al.*, 2004
β-elemene **(89)**	*P. spicatus*, *P. pennatifolius*	Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2002 Santos *et al.*, 2004
bicyclogermacrene **(90)**	*P. spicatus*, *P. pennatifolius*	Andrade Neto *et al.*, 2002 Santos *et al.*, 2004
elemol **(91)**	*P. spicatus*	Andrade Neto *et al.*, 2002
β-eudesmol **(92)**	*P. spicatus*	Andrade Neto *et al.*, 2002
cyclosativene **(93)**	*P. spicatus*	Andrade Neto *et al.*, 2002
caryophyllene oxide **(94)**	*P. trachyllophus*, *P. spicatus*	Andrade Neto *et al.*, 1995 Santos *et al.*, 1997 Andrade Neto *et al.*, 2000, 2002
α-humulene **(95)**	*P. microphyllus*, *P. trachyllophus*, *P. spicatus*, *P. grandiflorus*, *P. pennatifolius*	Craveiro *et al.*, 1979 Andrade Neto *et al.*, 1995 Santos *et al.*, 1997 Andrade Neto *et al.*, 2000, 2002 Santos *et al.*, 2004
α-copaene **(96)**	*P. microphyllus*, *P. spicatus*, *P. pennatifolius*	Craveiro *et al.*, 1979 Andrade Neto *et al.*, 2002 Santos *et al.*, 2004
β-borbonene **(97)**	*P. trachyllophus*, *P. pennatifolius*	Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2002 Santos *et al.*, 2004
β-caryophyllene **(98)**	*P. microphyllus*, *P. trachyllophus*, *P. spicatus*, *P. pennatifolius*	Craveiro *et al.*, 1979 Andrade Neto *et al.*, 1995 Santos *et al.*, 1997 Andrade Neto *et al.*, 2000, 2002 Santos *et al.*, 2004

TABLE VI - Terpenoids isolated from *Pilocarpus* species (continuation)

Terpene (class)	Species	References
Sesquiterpenes		
α-guaiaene **(99)**	*P. microphyllus*	Craveiro *et al.*, 1979
spathulenol **(100)**	*P. trachyllophus*, *P. pennatifolius*	Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2000 Santos *et al.*, 2004
α-cubebene **(101)**	*P. spicatus*	Andrade Neto *et al.*, 2002
allo-aromadendrene **(102)**	*P. spicatus*	Andrade Neto *et al.*, 2002
globulol **(103)**	*P. spicatus*	Andrade Neto *et al.*, 2002
viridiflorol **(104)**	*P. spicatus*	Andrade Neto *et al.*, 2002
guaiol **(105)**	*P. spicatus*	Andrade Neto *et al.*, 2002
bulnesol **(106)**	*P. spicatus*	Andrade Neto *et al.*, 2002
Diterpenes		
sandaracopimaradiene **(107)**	*P. jaborandi*	Craveiro *et al.*, 1979
angustifolin **(108)**	*P. riedelianus*	Guerreiro *et al.*, 2001
Triterpenes		
β-amyrin **(109)**	*P. grandiflorus*	De Souza *et al.*, 2003
β-amyrin acetate **(110)**	*P. trachyllophus*	Bertrand *et al.*, 2001
ocotillone **(111)**	*P. grandiflorus*	De Souza *et al.*, 2003
3-β-acetoxy-24-methyl-25-ethyl-20,24-epoxydammarane **(112)**	*P. spicatus*	Andrade Neto *et al.*, 1994
3-oxo-24-methyl-25-ethyl-20,24-epoxydammarane **(113)**	*P. spicatus*	Andrade Neto *et al.*, 1994
germanicol **(114)**	*P. grandiflorus*	De Souza *et al.*, 2003
Steroids		
β-sitosterol **(115)**	*P. grandiflorus*	De Souza *et al.*, 2003
β-sitosterone **(116)**	*P. grandiflorus*	De Souza *et al.*, 2003
7-oxo-β-sitosterol **(117)**	*P. grandiflorus*	De Souza *et al.*, 2003
stigmast-3,7-dione **(118)**	*P. grandiflorus*	De Souza *et al.*, 2003
7-β-hydroxy-stigmast-4-en-3-one **(119)**	*P. grandiflorus*	De Souza *et al.*, 2003
Polyprenols		
12-prenol **(120)**	*P. trachyllophus*	Bertrand *et al.*, 2001
[3*E*, 9*Z*]-13-prenol **(121)**	*P. trachyllophus*	Bertrand *et al.*, 2001
[3*E*, 10*Z*]-14-prenol **(122)**	*P. trachyllophus*	Bertrand *et al.*, 2001

The pattern of *n*-alkanes is considered an important taxonomic marker in plant classification accordingly to Eglinton *et al.* (1962). The *n*-alkanes identified in leaf epicuticular waxes of different *Pilocarpus* species with a carbon chain ranging from C_{14} to C_{33} (Skorupa *et al.*, 1998). An aromatic hydrocarbon (C_{20}) was detected only in *P. jaborandi* and this substance was considered a marker for the species (Negri *et al.*, 1998).

CONCLUDING REMARKS

In this review, information concerning the occurrence and pharmacological activities of secondary metabolites isolated from *Pilocarpus* spp were collected. Alkaloids, coumarins, flavonoids and terpenoids are current compounds to this genus (*Guerreiro et al.*, 2001). Compounds derived from *L*-phenylalanine are predominant in this genus.

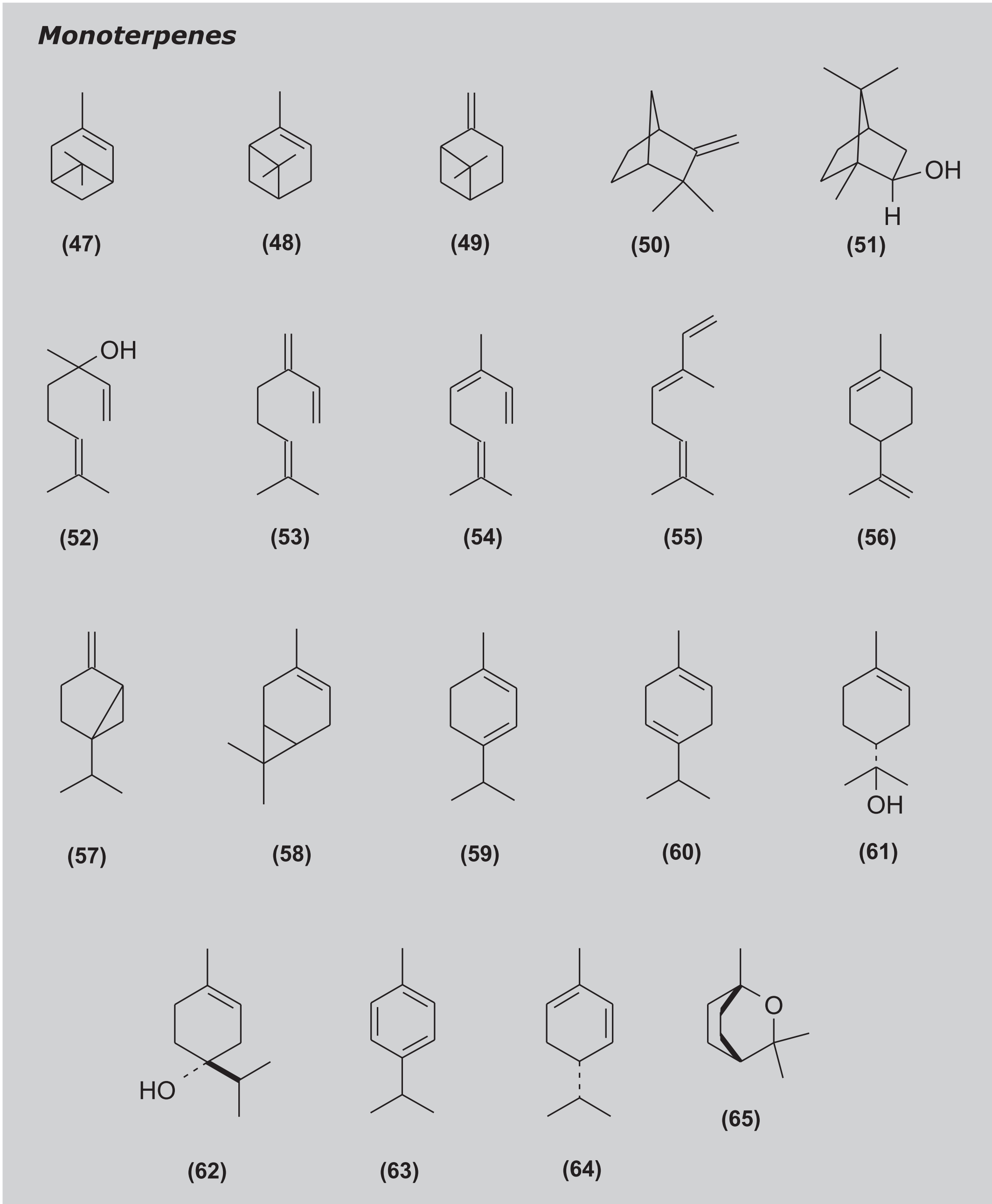


FIGURE 4 – Chemical structures of some terpenoids isolated from *Pilocarpus* species.

Although the medicinal value of pilocarpine is widely recognized, but the importance of other secondary metabolites obtained from *Pilocarpus* species was not yet well described. The summary of the main bioactive compounds, other than pilocarpine, described for *Pilocarpus* species are listed below:

1. From the 16 known *Pilocarpus* species, alkaloids have only been described in eight species (almost 1 alkaloid/species) (Table III), and for the majority of them the bioactivity was not yet determined;
2. There are a few reports over the presence of coumarins in *Pilocarpus* spp., however the pharmacological activities of this class o f compounds are numerous;
3. Flavonoids have been increasingly described as antioxidant drugs but these compounds were only found in *P. trachyllophus* (Table V);
4. Only two lignans were isolated from two *Pilocarpus* species and one of them has been described as an antichagasic agent (Table VII).

The use of plants in folk medicine has lead scientists

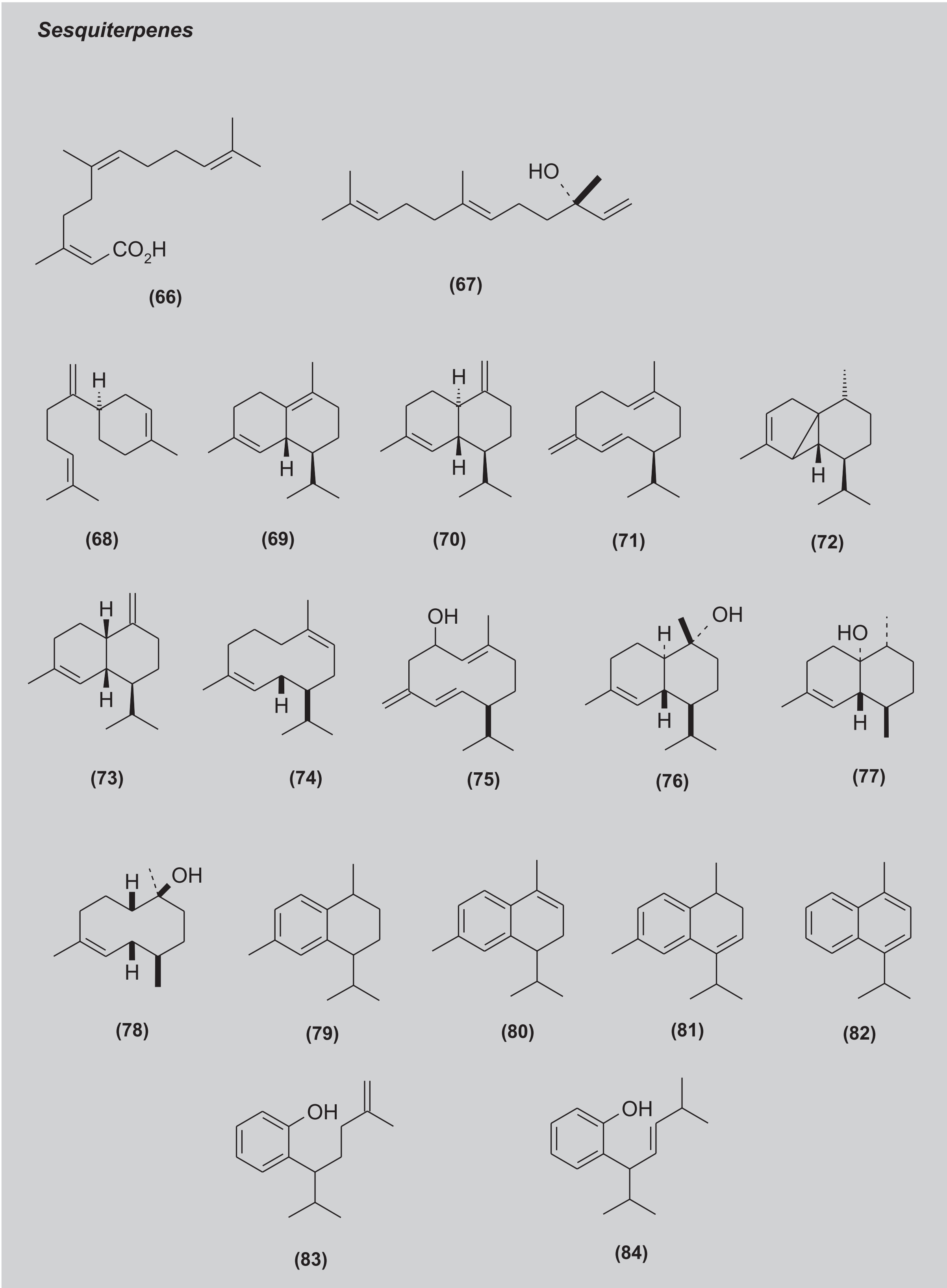


FIGURE 4 – Chemical structures of some terpenoids isolated from *Pilocarpus* species (continuation).

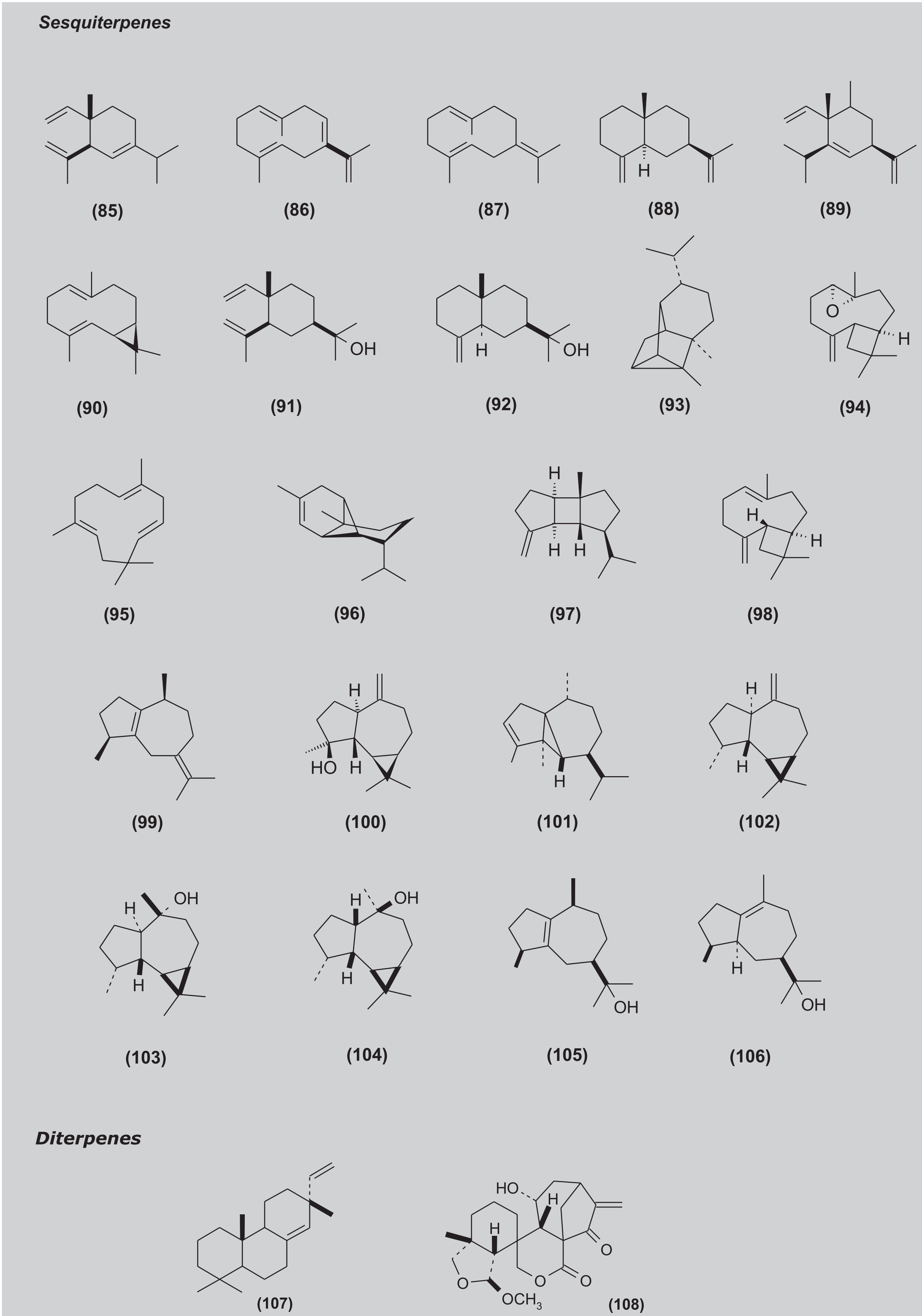


FIGURE 4 – Chemical structures of some terpenoids isolated from *Pilocarpus* species (continuation).

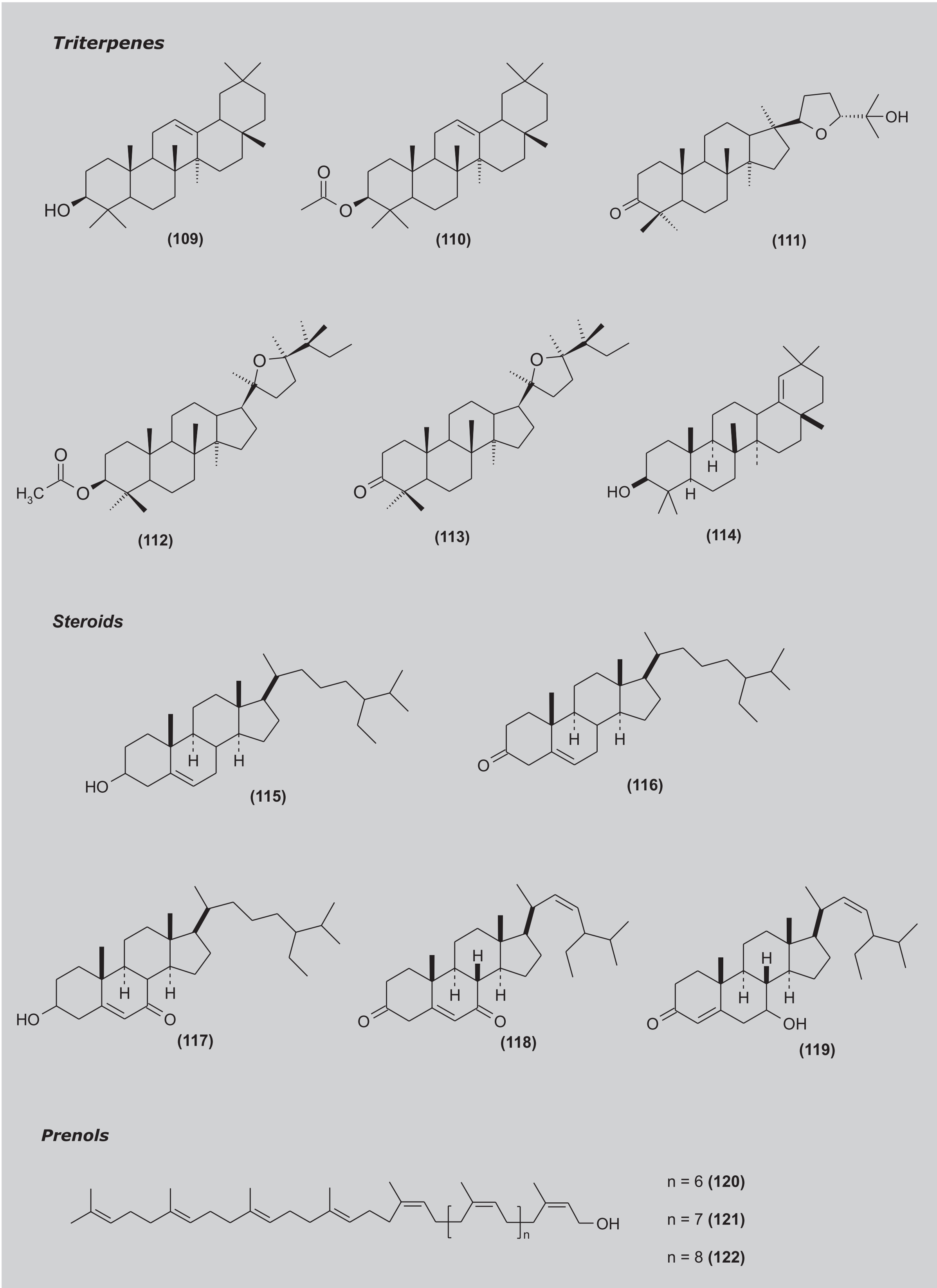


FIGURE 4 – Chemical structures of some terpenoids isolated from *Pilocarpus* species (continuation).

TABLE VII – Miscellaneous secondary metabolites isolated from *Pilocarpus* species and their respective biological activities

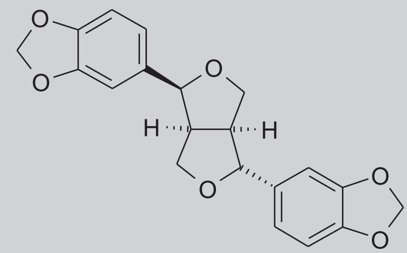
Compound	Species	Activity	References
(-)-episesamin **(123)**	*P. trachyllophus*	-	Andrade Neto *et al.*, 1995
lirioresinol B **(124)**	*P. grandiflorus*	Antichagásica	De Souza *et al.*, 2003 Sauvain *et al.*, 1996
pellitorine **(125)**	*P. trachyllophus*	Inseticida	Andrade Neto *et al.*, 1995 He *et al.*, 2002
eugenol **(126)**	*P. pennatifolius*	Inseticida Anestésica Antioxidante Antifúngica	Santos *et al.*, 2004 Park *et al.*,2000 Ogata *et al.*, 2000 Priyadarsini *et al.*, 1998 Meepagala *et al.*, 2002
N',*N*'-dimethyl antranilic acid **(127)**	*P. grandiflorus*	-	De Souza *et al.*, 2003
vanilic acid **(128)**	*P. grandiflorus*	-	De Souza *et al.*, 2003
siringaldehyde **(129)**	*P. grandiflorus*	-	De Souza *et al.*, 2003
2-undecanone **(130)**	*P. spicatus* *P.trachyllophus* *P. jaborandi*	-	Santos *et al.*, 1997 Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2000, 2002
2-tridecanone **(131)**	*P. spicatus* *P.trachyllophus* *P. jaborandi*	-	Santos *et al.*, 1997 Andrade Neto *et al.*, 1995 Andrade Neto *et al.*, 2000, 2002
1-hydroxy-2-tridecanone **(132)**	*P. trachyllophus*	-	Andrade Neto *et al.*, 1996
2-hydroxy-ethyl-glutarate **(133)**	*P. racemosus*	-	Compagnone & Rodriguez, 1993
methyl hexadecanoate **(134)**	*P. pennatifolius*	-	Santos *et al.*, 2004
hexanol **(135)**	*P. pennatifolius*	-	Santos *et al.*, 2004
undecanol **(136)**	*P. pennatifolius*	-	Santos *et al.*, 2004
1-phenyl-5-vinyl-5,9-dimethyl-decane **(137)**	*P. jaborandi*	-	Negri *et al.*, 1998 Skorupa *et al.*, 1998
tridecane **(138)**	*P. pennatifolius*	-	Santos *et al.*, 2004
pentadecane **(139)**	*P. pennatifolius*	-	Santos *et al.*, 2004
n-alcanes **(140)**	*P. alatus*, *P. carajaensis*, *P. giganteus*, *P. sulcatus,* *P. pauciflorus*, *P. jaborandi*, *P. grandiflorus*, *P. riedelianus*, *P. microphyllus*	-	Skorupa *et al.*, 1998

to find a wide variety of active substances of invaluable importance to mankind. Considering the variety of metabolites isolated from *Pilocarpus*, these species represent a vast research field to be exploited.

RESUMO

Pilocarpus spp.: Revisão sobre sua constituição química e atividades biológicas

Espécies de Pilocarpus *têm sido exploradas como única fonte do alcalóide imidazólico pilocarpina (utilizado no tratamento do glaucoma) desde o isolamento dessa substância até os dias atuais. A maioria das espécies de* Pilocarpus *conhecida é nativa do Brasil e, devido à importância medicinal que a pilocarpina possui e ao desmatamento, várias se encontram em risco de extinção. Outros metabólitos secundários entre os quais cumarinas, flavonóides e terpenos foram descritos em espécies desse gênero. Nesta revisão foram relacionados os metabólitos secundários isolados em diversas espécies de* Pilocarpus *bem como suas atividades biológicas. Apesar da varieda-*



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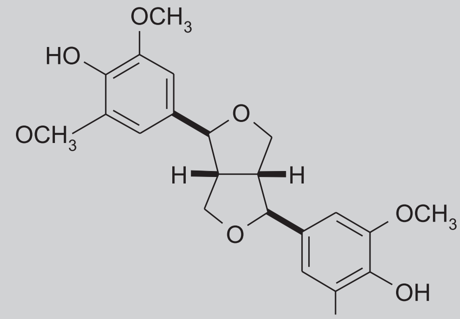

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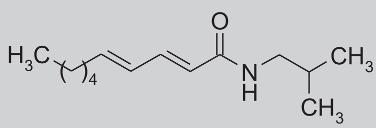

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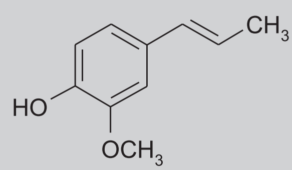

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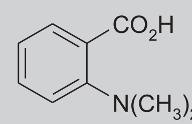

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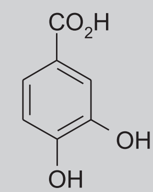

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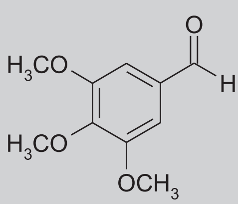

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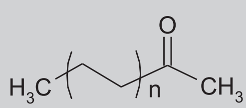
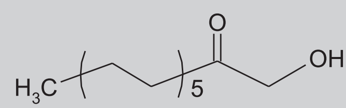


n=4 **(130)**

n=5 **(131)**



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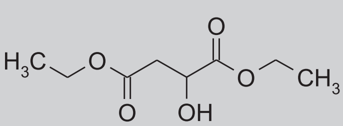

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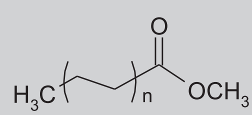
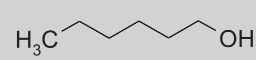


n = 7 **(134)**



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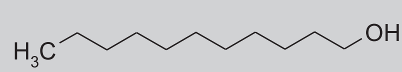

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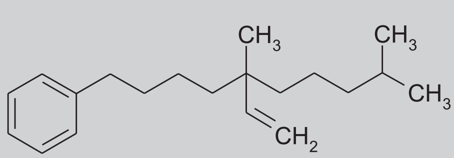

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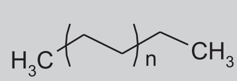
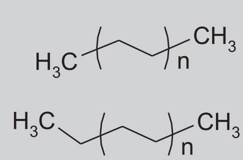


n = 5 **(138)**
n = 6 **(139)**



n = 6- 15 **(140)**

FIGURE 5 – Chemical structures of miscellaneous secondary metabolites isolated from *Pilocarpus* species.

de de estruturas e as importantes atividades biológicas já descritas na literatura para as outras classes de metabólitos secundários, ainda há um vasto campo de estudo para as espécies de Pilocarpus.

UNITERMOS: Rutaceae. Pilocarpus spp. Metabólitos secundários. Atividades biológicas.

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