An Acad Bras Cienc (2023) 95(Suppl. 1): e20211488 DOI 10.1590/0001-3765202320211488
Anais da Academia Brasileira de Ciências | *Annals of the Brazilian Academy of Sciences*
Printed ISSN 0001-3765 I Online ISSN 1678-2690
www.scielo.br/aabc | www.fb.com/aabcjournal

CHEMICAL SCIENCES

Bioactive natural products from orchids native to the Americas - A review

ARMANDO MATEUS POMINI, SANDRA APARECIDA SAHYUN, SILVANA MARIA DE OLIVEIRA & RICARDO TADEU DE FARIA

Abstract: The purpose of this review is to provide information on the traditional uses, phytochemical and pharmacological studies performed with species of orchids native to the Americas and the Caribbean Islands. The treatment of inflammation is the most traditional use for plants of this family, specially in Central America, while anti-inflammatory and anticancer assays are oftenly reported in pharmacological investigations. From the chemical point of view, they are sources of phenanthrenoids and stilbenes, rare secondary metabolites not commonly found in other families of plants, as well as cycloartane triterpenes, pyrrolizidine alkaloids and flavonoids. Since just few species were chemically and pharmacologically studied, in comparison to the large number of native species (less than 0.5% of the total), the orchids of the New World may be an interesting niche for the discovery of new, bioactive natural products.

Key words: Orchidaceae, neotropical, secondary metabolites, stilbene, phenanthrene, anti-inflammation.

INTRODUCTION

Orchidaceae is one of the most numerous families of flowering plants on the planet. With approximately 28,000 known species, orchids occur in virtually every region of the globe, except for Antarctica, the cold regions of northern Siberia and in desert areas with low rainfall (Chase et al. 2015). Many authors consider orchids as some of the most evolved plants on the planet, given their complex relationships with symbiotic organisms such as fungi and pollinators, and the great diversity of species and forms (Ramírez et al. 2011, Papadopulos et al. 2013, Stokstad 2015). Records point to ancestors of the orchids existing nearly one hundred million years ago, during the Cretaceous period (Ramírez et al. 2007).

Orchids have various vegetation patterns. Many species are terrestrial, especially those found in subtropical regions such as Europe and North America. There are also the rupicolines, which develop on rocks, and the saprophytes, which grow on decaying organic material. However, a significant number of orchids display epiphytic behaviour, particularly species that occur in tropical regions with high rainfall. Growing on trees, these plants live on condensed dew water, mineral salts carried by the wind to the tree trunks, animal faeces that eventually come into contact with the roots and, especially, nutrients made available by symbiotic fungi, which slowly degrade the wood of the trees on which they grow (Miller & Warren 1994). Despite great morphological diversity among the thousands of existing species, there are preserved floral patterns, such as the presence of three sepals and three petals, typical of monocots, where one of the petals is modified and given the name of labellum. The labellum generally protects or facilitates pollinator access to the column, an organ comprising a fusion of the gynoecium and androecium. The pollen is generally grouped in the form of pollinia, which are located on the column just above the stigma (Miller & Warren 1994). In addition, most orchids have elaborate systems for collecting and maintaining water. It is common for the leaves, rhizomes and pseudobulbs to present specific regions used for the water reserves of the plant. Orchid roots generally have a thick layer of velamen, a highly efficient water-collecting material (Miller & Warren 1994).

Orchids have been used by man as herbal remedies since time immemorial. Chinese medical material is full of species used for the most diverse purposes. Several species of genera *Dendrobium* and *Bletia* are widely used in a variety of medical applications. Traditionally, the chemistry of bioactive natural products from Asian orchids is widely developed, with Chinese and Indian species being among the best known from a chemical point of view (Sut et al. 2017).

However, the greatest number of known species is found in the New World. Over the last five centuries, the neotropics have been the source of several species of orchids that enchant the world for their beauty and exoticism. Species of genera *Cattleya*, *Laelia*, *Sophronitis*, *Oncidium*, *Brassavola*, *Miltonia* are widely used in ornamentation and hybridisation, with significant participation in the ornamental orchid market. Colombia, Ecuador and Brazil represent the countries with the greatest species diversity in the Americas and, with New Guinea in Asia, are among the four countries in the world having the greatest number of catalogued species (Govaerts et al. 2018). Many species are endemic, thanks mainly to the extensive areas of forest in the Amazon and the great biological diversity of the Atlantic Forest of South America and the Central American forests.

From an historical point of view, species of genus *Vanilla* have been used by local American populations for hundreds of years due to the intense vanilla aroma of their berries and seeds. Rich in vanillin, a simple phenolic aldehyde, this natural product was taken to Europe by Spanish colonisers and was one of the first areas of interest in the bioactive natural products of orchids from the neotropics (Menon & Nayeem 2013).

Some species of orchids from South America are used in folk medicine, a small number compared to the diversity and expression of the family on the continent. Species of genus *Cyrtopodium*, popularly known as 'sumarés', are used by indigenous populations to treat burns and inflammation arising from muscle contusions. Reports of the use of orchids as medicinal plants in folk medicine are more common in Central America, more specifically in Mexico, where indigenous populations report the use of several species, principally in anti-inflammatory preparations (Garcia et al. 2014, Schultes 1979).

Despite being well known from a horticultural point of view, little is known about the chemical and pharmacological potential of native orchids from the Americas. This is the opposite to that seen with orchid species from Asia, especially from China, since local populations have been using native orchids as herbal medicines for millennia, which has surely helped stimulate the in-depth phytochemical and pharmacological study of local plants (Gutierrez 2010). Orchids comprise the most diverse group in the Americas, with around 12,983 distinct species. On average, 744 species new to science are described per year (Pesquisa Fapesp 2018). The present review counted approximately 50 species native to the Americas studied phytochemically using modern spectroscopic techniques (mainly mass spectrometry and nuclear magnetic resonance), in studies that have led to the structural identification of non-volatile secondary metabolites. However, the number of pharmacological studies of these plants and metabolites is considerably less. In-depth chemotaxonomic considerations have been found in only one publication to date (Savaris et al. 2018).

These data show that much research remains to be done to better understand the chemical aspects of orchids native to this region, including the potential discovery of new biologically active molecules. As can be seen throughout this review, the chemical study of American orchids has very often led to the identification of several metabolites that were unprecedented in their time, clearly demonstrating the enormous chemical potential of these plants. Another factor to be considered is the constant threat to orchids from the development of human activity. Many species and varieties of orchids are endemic to certain ecological niches, often from small areas, and are therefore threatened by the expansion of cities and agriculture. Dramatic examples are the forests of the Florida coast (USA) and the region of South American Atlantic Forest, which over the last few centuries have undergone a large reduction in area, giving way to the most densely populated regions of Brazil (Ribeiro et al. 2009). Fortunately, recent years have seen a growing understanding of the need to protect orchids in their natural environment, either through natural parks or even through the collection and rescue of specimens that inhabit places subject to major engineering works, such as large agricultural projects or artificial dams for the construction of hydroelectric plants. Knowledge of the phytochemical and pharmacological potential of these species is an important argument that helps emphasise the need for their preservation.

This review is therefore organised by the classes of chemical compounds most commonly found in studies of native orchids from the American continent, highlighting the most common or most differentiated in terms of structure, and seeking to establish a pharmacological and ethnopharmacological relationship for the various species under study. Comprehensive relationships between the main classes of secondary metabolites isolated from species of different subtribes, as well as the ethnopharmacological uses of species native to the American continent and the Caribbean, are shown in Tables I and II.

XANTHONES

Xanthones are metabolites that are rarely found in neotropical orchids. The recent chemical study of the *Maxillaria picta*, native to southern Brazil, resulted in the isolation of large amounts of C-glycosylated xanthone mangiferin (**1**) (Almeida et al. 2014). In an extensive study using chromatographic techniques, it was reported that the species *Maxillaria luteo-alba*, the Mexican species *Mormolyca rigens*, and several species of genus *Polystachia* also contain the xanthones mangiferin (**1**) and isomangiferin (**2**) in their extracts (Williams 1979) (2). In evaluations of *in-vitro* biological activity against the neotropical parasites *Leishmania amazonensis* and *Trypanosoma cruzi*, compound **1** isolated from *M. picta* showed no activity until high concentrations were tested. However, studies indicate that compound **1** shows several significant biological activities, such as a chemopreventive and anti-inflammatory (Jyotshna et al. 2016).

Table I. Summary of the ethnobotanical and pharmacological data on American orchids found in the review.

Species of Orchid	Ethnopharmacological use	Pharmacology	Reference
Arethusa bulbosa	Relieves toothache		Castle 1886
Arpophyllum spicatum	To treat dysentery		Ossenbach 2009 Hossain 2011
Bletia campanulata	To treat dysentery		Ossenbach 2009 Hossain 2011
Bletia purpurea	Stomach tonic antidote for fish poisoning		Hossain 2011
Broughtonia domingensis	Infections Kidney disorders		Bond et al. 2014
Bromheadia finlaysoniana	Relief of body pain		Hossain 2011
Bulbophyllum vaginatum	Earache		Hossain 2011
Catasetum maculatum	Healing wounds, curing tumours		Ossenbach 2009
Cranichis speciosa	Dysentery		Hossain 2011
Cypripedium parviflorum	Hysteria and disorders of the nervous system		Teoh 2019
Coeloglossum viride var. *bracteatum*		Improves learning and memory in rats with IBO-induced dementia the action can be attributed to increased activity and ChAT expression in the brain. Anti-ageing dementia	Zhong et al. 2019
Corallorhiza odontorhiza	Used as a diaphoretic and febrifuge in serious illness		Hossain 2011
Corallorhiza maculata	Increases the blood in patients with pneumonia		Hossain 2011
Cypripedium sp.	Antispasmodic sedatives Fights insomnia and nervous tension. Treatment of insomnia, anxiety, fever, headache, neuralgia, emotional tension, palpitations, tremors, irritable bowel syndrome, delirium, seizures due to fever, relieving the pain of menstruation and childbirth. Antispasmodic, anodyne, diaphoretic, hypnotic, nervous action, sedative, stimulant and tonic.		Wilson 2007
Cyrtopodium andersonii		Anti-inflammatory and anti-ulcer activity	Parente et al. 2014
Cyrtopodium cardiochilum		Inhibits capillary permeability and demonstrates phagocytosis-stimulating properties.	Barreto & Parente 2006
Cyrtopodium glutiniferum	Treatment of abscesses and healing wounds.	Positive anti-inflammatory and anti-proliferative effects of the extract against activated mononuclear cells.	Araujo-Lima et al. 2020
Cyrtopodium macrobulbon	Analgesic and anti-inflammatory of the urinary tract. Treatment of painful urinary disease (‘mal de orin’).	Several isolated compouns have known antinociceptive activity.	Morales-Sánchez et al. 2014
Cypripedium parviflorum	Hysteria and disorders of the nervous system		Teoh 2019
Cypripedium puncttum	Broken bones, coughing, kidney disease.		Bond et al. 2014

Table I. Continuation.

Cyrtopodium paniculatum		Showed low activity against U-87 human glioblastoma cells.	Auberon et al. 2017
Epidendrum pastoris	Dysentery		Hossain 2011
Epidendrum chlorocorymbos	Used for reducing blood cholesterol levels, stimulating sleep, healing blemishes, earache.	A strong antinociceptive	Asseleih et al. 2015
Epidendrum mosenii	Treatment of pain and infections	Antinociceptive activity	Rosa et al. 2007, 2008
Epidendrum mosenii	Used in folk medicine for therapeutic purposes, especially to treat pathologies related to painful and infectious processes	Analgesic effect; has toxic effects that could compromise its therapeutic uses, but preliminary results revealed no toxicity in rats.	Floriani et al. 1998
Epidendrum mosenii		Showed interesting hypoglycemic activity in the test for induced diabetes using alloxane in rats. Analgesic activity demonstrated in the trial for abdominal contortions induced by acetic acid. Antifungal activity against the microorganisms: *Cryptococcus neoformans* Microsporum gypseum Trychophyton rubrum Trychophyton metagrophytes	Novaes et al. 2001
Encyclia citrina	Infected wounds		Hossain 2011
Encyclia pastoris	Dysentery		Ossenbach 2009
Euchile citrina	Treatment of infected wounds		Ossenbach 2009
Gomesa recurva		Activity against HeLa and Vero cells	Savaris et al. 2018
Habenaria floribunda	Vaginal bleeding	Antioxidant activity	Asseleih et al. 2015
Isochillus latibracteatus	Indicated as a therapeutic application for 'latido' (pain in the pit of the stomach) and 'ventazón' (a kind of colitis)		Asseleih et al. 2015
Isochillus major	The leaves are used in the case of contusions Applied as a poultice for inflammation		Asseleih et al. 2015
Laelia anceps	Treatment for postpartum pain in mexican folk medicine	Anti-hypertensive Induces vasorelaxant and antihypertensive effects by blocking the $Ca^{(2+)}$ channels	Vergara-Galicia et al. 2010a
Laelia autumnalis	Coughing To reduce postpartum pain		Hossain 2011
Laelia autumnalis	Coughing		Ossenbach 2009

Table I. Continuation.

Laelia marginata		Biological assays with crude plant extract, fractions and isolated compounds were carried out against two human cancer cell lines (Hela and Siha), in addition to the tropical parasites *Trypanosoma cruzi* and *Leishmania* (leishmania) *amazonensis*. 9,10-dihydro-4-methoxy-phenanthrene-2,7-diol was active against Hela and Siha cells. The flavone rhamnazin was not able to recover the viability of Vero cells infected with the Zika virus.	Belloto et al. 2017
Laelia marginata		Antiproliferative activity against cancer cells modified by Hela and Siha HPV.	Williams et al. 2012
Maxillaria densa	Spasmolytic activity		Estrada et al. 1999
Maxillaria densa		Induces relaxation via an endothelium-independent pathway by blocking the calcium channels and opening the potassium channels in the myogenic response of rat aortic rings	Rendon-Vallejo et al. 2012
Maxillaria densa	Gastrointestinal problems		Rendón-Vallejo et al. 2012 , Ramírez-Galicia et al. 2007, Déciga-Campos et al. 2007, Hernández-Romero et al. 2004, Estrada et al. 2004
Maxillaria densa	Prevention of abortion Control of ectoparasites		Déciga-Campos et al. 2007a, Déciga-Campos et al. 2007b
Maxillaria densa		*In-vivo* antinociceptive effect *In-vivo* antinociceptive and anti-inflammatory effect	Déciga-Campos 2007b
Maxillaria densa		*Ex-vivo* vasorelaxant activity	Rendón-Vallejo et al. 2012
Maxillaria densa		*In-vitro* spasmolytic activity	Estrada et al. 2004, Estrada et al. 1999, Mata et al. 2014
Maxillaria picta		Showed cytostatic activity against several human cancer cell lines and effective activity on the viability of different forms of the parasites *T. cruzi* and *L. amazonensis*	Almeida et al. 2014
Myrmecophila tibicinis	Help during childbirth (‘hom-ikim’)		Ossenbach 2009
Miltonia flavescens		Antifungal. Active against seven human cancer cell lines, including NCI-ADR-RES ovarian sarcoma, with an IC50 value of 2.6μg/mL. First report of the cytostatic activity of this flavone against human ovarian sarcoma.	Porte et al. 2014

Table I. Continuation.

Mormodes maculata var. *unicolor*	Applied as a poultice to treat inflammation of affected areas of the body due to abrupt movements, such as a twisted ankle.		Asseleih et al. 2015
Oeceoclades maculata		Antioxidant activity of extracts and fractions of the plant. Stomach problems.	Carrera et al. 2014, Bond et al. 2014
Oestlundia luteorosea	Used in traditional medicine to reduce or alleviate head pain.		Asseleih et al. 2015
Oncidium baueri		Antiproliferative activity against several human cancer cell lines, with emphasis on kidney cancer cells.	Monteiro et al. 2014
Oncidium ascendens	For inflammation caused by the introduction of sharp implements also used for 'limpias' (a kind of cleansing of the body and soul, using the plant to brush the body).	Biological activities such as the inhibition of cancer cell lines. Induction of apoptosis.	Asseleih et al. 2015
Oncidium cebolleta	Medicinal hallucinogen	To treat pain and inflammation in muscle contusions	Ossenbach 2009, Stermitz et al. 1983
Oncidium isthmi		Active against lung cancer cells with the induction of apoptosis	Williams et al. 2012
Phragmipedium calurum		Antiproliferative activity against multiple human cancer cell lines, with two exhibiting moderate activity against multiple cell lines	Courtney et al. 2012
Pleurothallis cardiothallis	Contraceptive and abortive activity		Mó & Ix 2015
Prosthechea karwinskii	In the treatment of coughing (infusions), wounds and burns (poultices), diabetes (tea or chewed), and to prevent miscarriages and assist childbirth (infusions).		Cruz Garcia et al. 2014
Prosthechea karwinskii		Promotes the inhibition of reactive oxygen species, anti-inflammatory effect without inducing gastric damage in animals.	Barragán-Zarate et al. 2020
Prosthechea michuacana	Anti-inflammatory activity	Antioxidant	Gutierrez et al. 2010, Gutierrez 2010
Prosthechea michuacana		Hypoglycemic activity through the improvement of hyperlipidemia resistant to insulin. Prevents oxidative stress induced by hyperglycemia in the pancreas.	Gutierrez et al. 2013
Prosthechea michuacana		Nephroprotective activity	Gutierrez et al. 2010
Prosthechea michuacana		Hepatoprotective activity	Gutierrez et al. 2011
Ponthieva racemosa	Respiratory problems		Duggal 1971
Scaphyglottis livida		Anti-inflammatory and antinociceptive activity	Déciga-Campos et al. 2007
Sobralia macrantha	Fever		Hossain 2011
Scaphyglottis fasciculata	Anti-abortive	Anti-inflammatory Antinociceptive and relaxant activity	Asseleih et al. 2015
Spathoglottis plicata	As a hot poultice for the treatment of joint pain		Hossain 2011
Spiranthes eriophora	For the treatment of asthma	Antioxidant activity	Asseleih et al. 2015

Table I. Continuation.

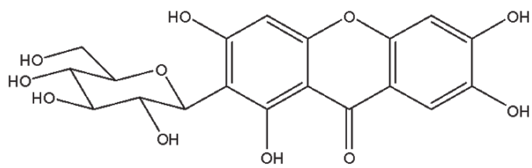
Stanhopea lietzei		Biological assays against neotropical parasites, viruses and human cancer cell lines. Isolated biphenanthrene with anticancer activity.	Lucca et al. 2021
Stanhopea hernandezii	To treat tiredness		Ossenbach 2009
Stanhopea hernandezii	Sunstroke		Hossain 2011
Stanhopea oculata	Reduction of the abdomen (belly) To treat pain in women	Confirmed anti-fatigue activity.	Asseleih et al. 2015
Vanda hookeriana	Used as a hot poultice for the treatment of joint pain		Hossain 2011
Vanilla dilloniana	To stimulate the appetite To aid diggestion		Bond et al. 2014
Vanilla planifolia	Hysteria, fever, impotence, rheumatism and to increase the energy of the muscular system		Hossain 2011
Vanilla planifolia	High fever To aid digestion Appetiser Aphrodisiac Diuretic	Confirmed biological activities: antioxidants, anti-inflammatory, anti-cancer, against cellular stress, antimicrobial, anti-cholesterol, antinociceptive, antidepressant and acetyl cholinesterase inhibition (Alzheimer)	Asseleih et al. 2015, Ossenbach 2009
Vanilla planifolia		Anticlastogenic properties Ability to reduce chromosomal damage caused by X-rays and UV light Antimutagenic Anticarcinogenic effects on a family of DNAPK inhibitors Other types of cancers Antimicrobial properties against yeasts Effective inhibitor of red sickle cells in patients with sickle cell anaemia Aphrodisiac activity Antioxidant activity	Menon & Nayemm 2013, Shanmugavalli et al. 2009

ALKALOIDS

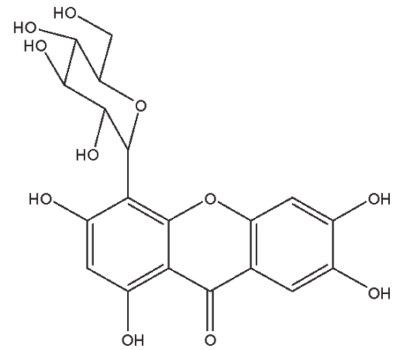
One marked difference seen in phytochemical studies of neotropical orchids, is the small number of reports of the occurrence of alkaloids compared to Asian species (Carrera et al. 2014, Lünning, 1964). Chemical study of the species *Pleurothallis johannensis*, *P. teres*, *P. reata* and *P. fabiobarrosii*, collected in both southeastern and northeastern Brazil, revealed the presence of the alkaloid 1-hydroxymethylpyrrolizidine (**3**). The different concentrations of diastereoisomers of this alkaloid found in the above species provided ecophysiological clues that contributed to their taxonomic differentiation (Borba et al. 2001). Pyrrolizidine alkaloids have also been found in terrestrial North American orchids of genus *Liparis* from the subtribe Habenariinae (Lindström & Lünning 1971, Lindström & Lünning 1972).

Table II. **Main types of natural products commonly found in orchids native to the American continent and Caribbean, according to botanical tribe and subtribe.**

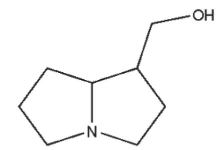
Tribe	Subtribe	Species (Reference)	Triterpenes	Diterpenes	Alkaloids	Phenanthrenoids	Bi-phenanthrenes	Stilbenes	Flavonoids	Xantohnes	Phenanthrene-furanes	Malic acid deriv.
Epidendreae	Laeliinae	*Laelia marginata* (Belloto et al. 2018)	X			X		X	X			X
		Laelia anceps (Vergara-Galicia el al 2010b)				X						
		Epidendrum rigidum (Hernández-Romero et al. 2005)	X			X		X	X			
		Scaphyglottis livida (Estrada-Soto et al. 2006)						X				
		Sophronitis coccinea (Tatsuzawa et al. 1998)							X			
		Sophronitis wittigiana (Tatsuzawa et al. 2014)							X			
		Encyclia longifolia (Bhattacharyet al. 2006)				X						
		Prosthechea michuacana (Gutierrez et al. 2010)	X	X		X	X	X	X			
		Prosthechea karwinskii (Garcia et al. 2014)							X	X		
		Prosthechea cochleata (Díaz-Avilés et al. 2020)	X		X				X			
		Prosthechea lívida (Díaz-Avilés et al. 2020)	X		X				X			
		Myrmecophila humboldtii (Williams et al. 2012)				X		X				
		Scaphyglottis livida ((Estrada et al. 2002)	X					X				
		Epidendrum mosenii (Rosa et al. 2008)				X		X				
		Nidema boothii (Estrada et al. 2002, Hernández-Romero et al. 2004)	X					X				
	Pleurothallidinae	*Pleurothallis johannensis, P. teres, P. ocreata, P.fabiobarrosii* (Borba et al. 2001)			X							
Cymbidieae	Cyrtopodiinae	*Cyrtopodium macrobulbon* (Morales-Sánchez et al.2014)				X		X				
		Cyrtopodium paniculatum (Auberon et al. 2016, Auberon et al. 2017)				X	X	X				
	Maxillariinae	*Maxillaria densa* (Déciga-Campos et al. 2007, Rendón-Vallejo et al. 2012, Estrada et al. 2004, Estrada et al. 1999)				X						
		Maxillaria picta (Almeida et al. 2014)	X					X		X		
		Mormolyca rigens (Williams et al. 1979)								X		
		Maxillaria luteo-alba (Williams et al. 1979)								X		
	Oncidiinae	*Oncidium baueri* (Monteiro et al. 2014)				X			X			
		Oncidium microchilum (Williams et al. 2012)				X		X			X	
		Oncidium isthmi (Williams et al. 2012)				X		X				
		Oncidium ceboletta (Stermitz et al. 1983)				X						
		Gomesa recurva (Savaris et al. 2018)				X						
		Miltonia flavescens (Porte et al. 2014)							X			
		Phymatidium falcifolium (Williams et al. 1994)							X			
		Zygostates cornuta, Z. alleinana, Z. luneta, Z. pelúcida, Z. pustulata, Z. grandiflora, Z. multiflora (Williams et al. 1994)							X			
		Ornytocephalus bicornis, O. kruegeri, O. myrticola (Williams et al. 1994)							X			
		Chytroglossa marileoniae (Williams et al. 1994)							X			
		Oncidium excavatum (Williams et al. 1979)							X			
		Rauhiella Silvana (Williams et al. 1994)							X			
		Oncidium sphacelattum (Williams et al. 1979)							X			
Orchideae	Orchidinae	*Habenaria petalodes* (Cota et al. 2008)							X			X
		Habenaria repens (Johnson et al. 1999, Wilson et al. 1999)										X
Cypripedioidea (*Subfamily)		*Phragmipedium calurum* (Starks et al. 2012)						X				
		Phragmipedium sp. (Garo et al. 2007)					X					



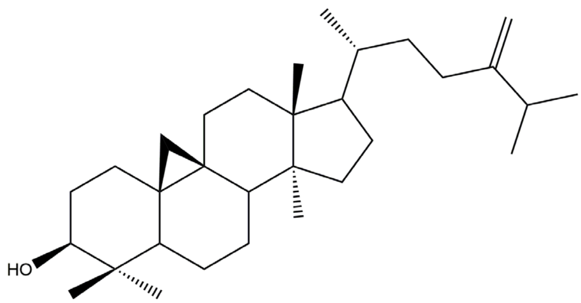
1



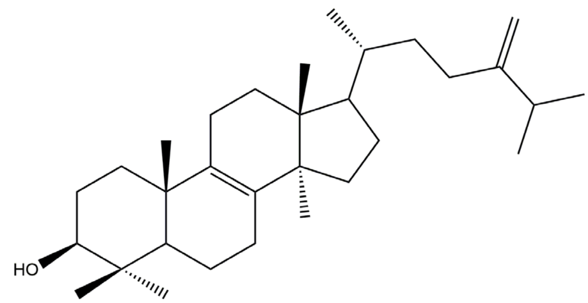
2



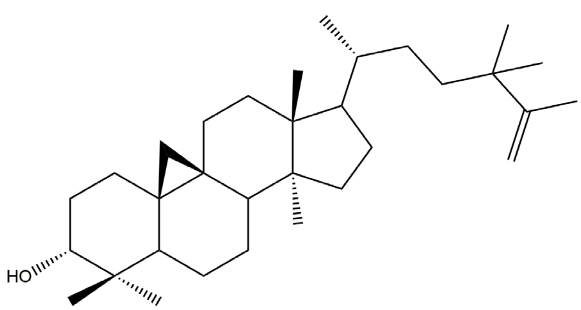
3



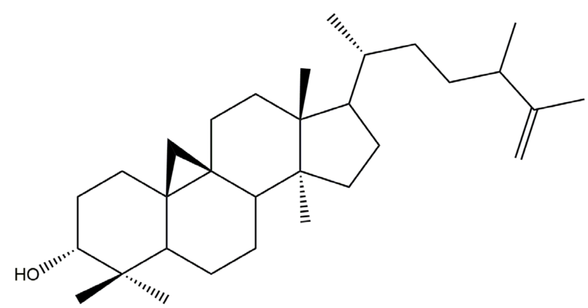
4



5



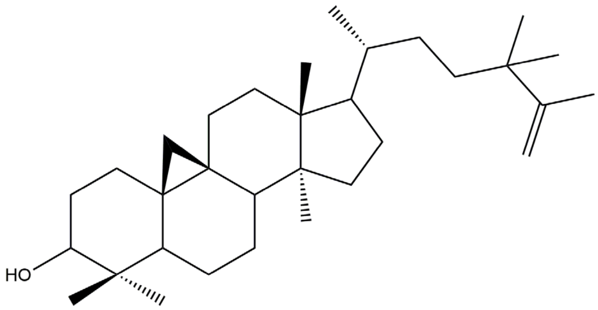
6



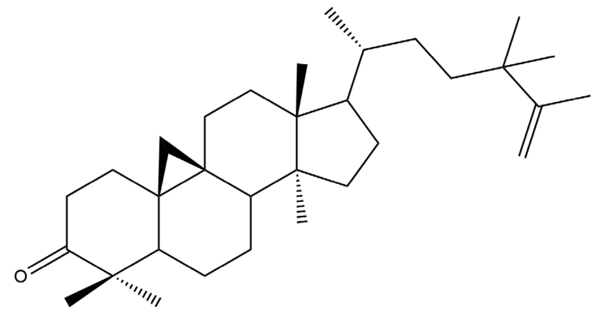
7

TRITERPENES AND DITERPENES

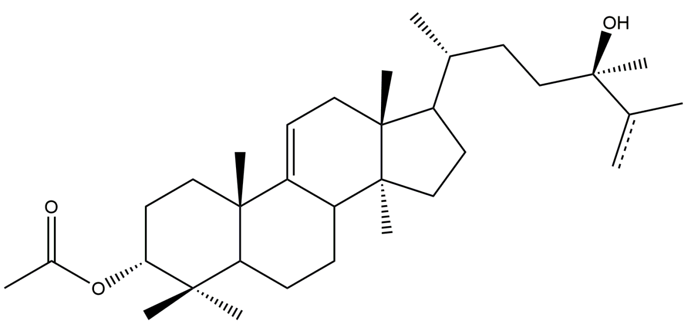
Triterpenes of the class of cycloartanes have been reported in some species of neotropical orchids. Chemical study of the species *Laelia marginata* and *Maxillaria picta*, native to southern Brazil, led to the identification of 24-methylenecycloartenol (**4**) (Almeida et al. 2014). The tissues of *M. picta* also contain the triterpene eburicol (**5**), a possible biosynthetic precursor of compound **4** (Belloto et al. 2018). Compound **4** was also reported in the species *Epidendrum mosenii*. This species is used by rural Brazilian populations to treat pain and infections. An ecophysiological study showed that *E. mosenii* contains compound **4** in each of the plant organs, and that the highest concentrations of this triterpene in the plant tissue occur during spring and summer (Rosa et al. 2007). The researchers further showed that the antinociceptive activity of the plant in mice is possibly related to the presence of compound **4**. The Mexican species *E. rigidum* also produces triterpenes of the class of cycloartanes (**6** and **7**) (Hernández- Romero et al. 2005).



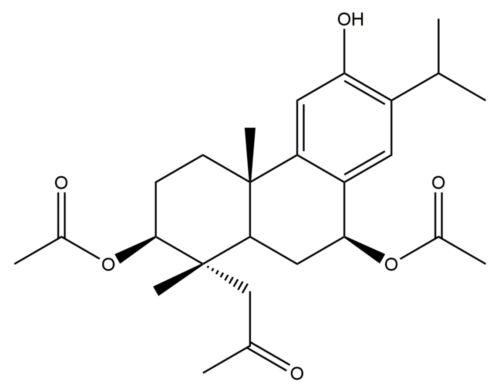
8



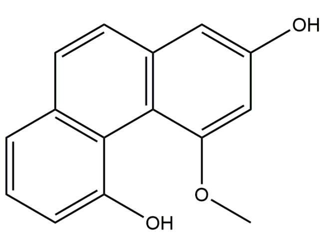
9



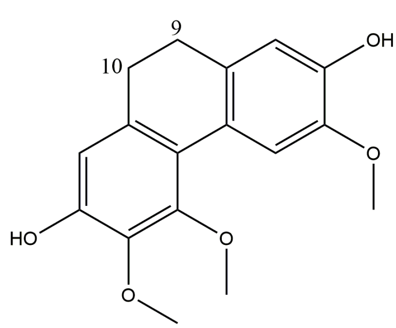
10 C=C
11 C-C



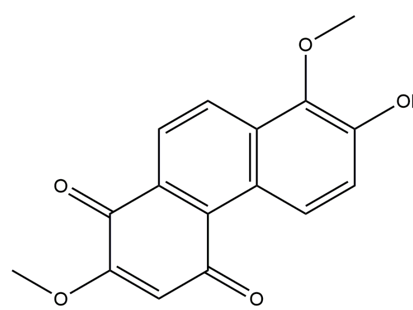
12



13



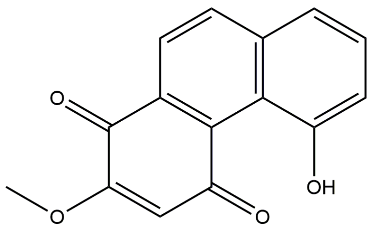
14



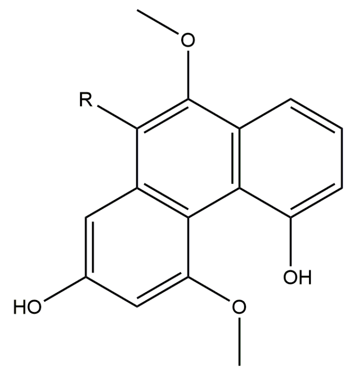
15

In-vivo studies have shown that the extract of the Mexican orchid *Scaphyglottis livida* shows significant anti-inflammatory activity, which explains its use for this purpose in Aztec traditional medicine. Two cycloartane triterpenes have been isolated from this plant, (**8**) 5-lanosta-24,24-dimethyl-9(11),25-dien-3-ol and (**9**) 24,24,dimethyl-9,19-cyclolanosta-9(11),25-dien-3-one (cyclobalanone), with compound **8** showing anti-inflammatory activity in mice in carrageenan-induced models (Déciga-Campos et al. 2007).

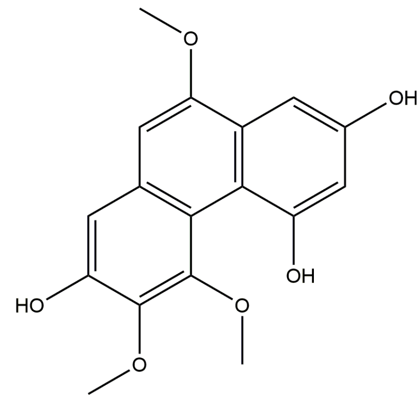
The orchid species *Prosthechea michuacana* has been used since pre-Columbian times by Mexican natives as food and in formulations showing anti-inflammatory activity. The chemical



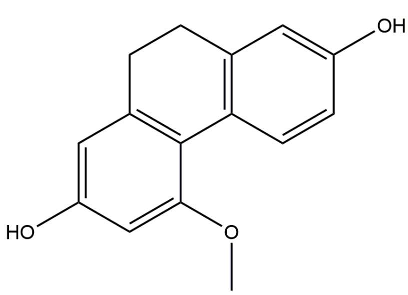
16



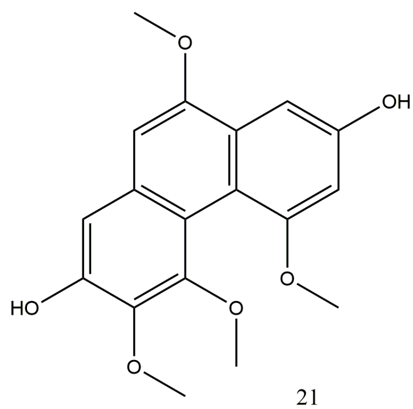
17 R = H
18 R = OCH_3



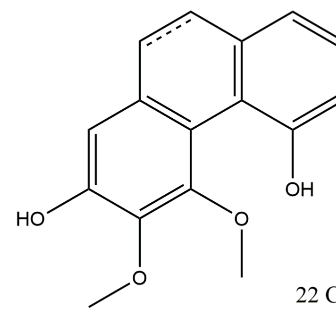
19



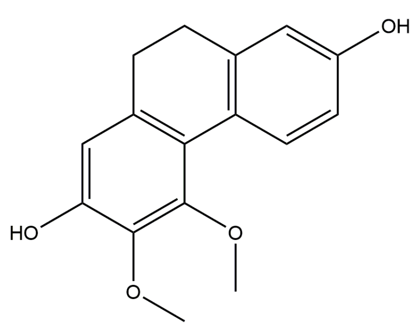
20



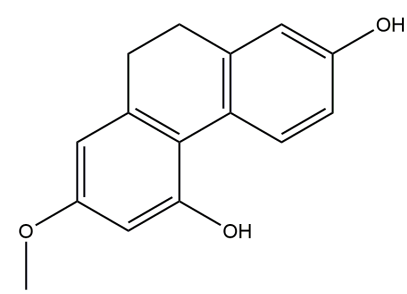
21



22 C=C
23 C-C

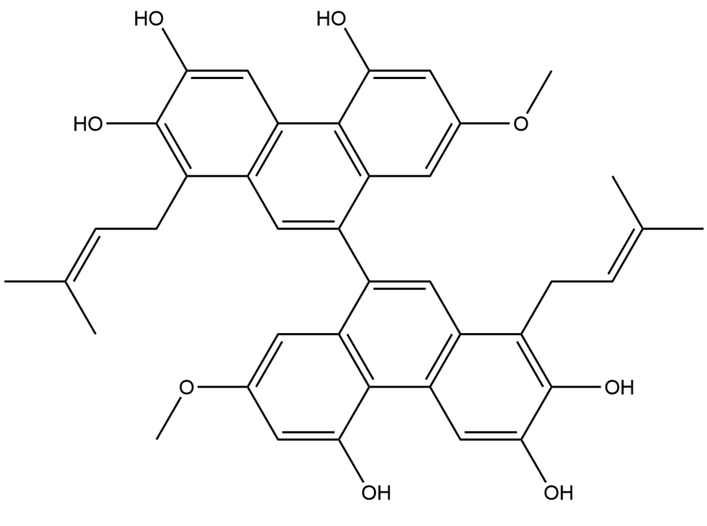


24

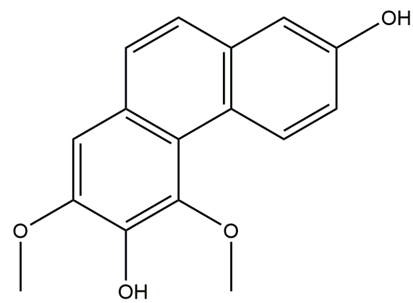


25

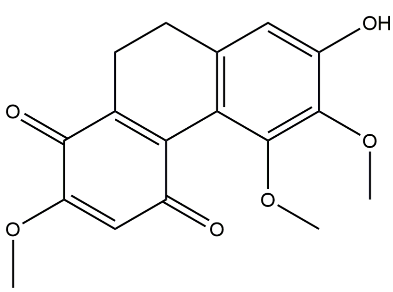
study of this species has resulted in the isolation of two lanostane-type triterpenes (**10** and **11**). Interestingly, this species also produces a diterpene of the class of triacetylated abiethanes (**12**), which showed free radical sequestration in DPPH assays, most likely due to the presence of a phenolic hydroxyl (Gutierrez 2010). To date, this is the only report of diterpene isolation in neotropical orchids.



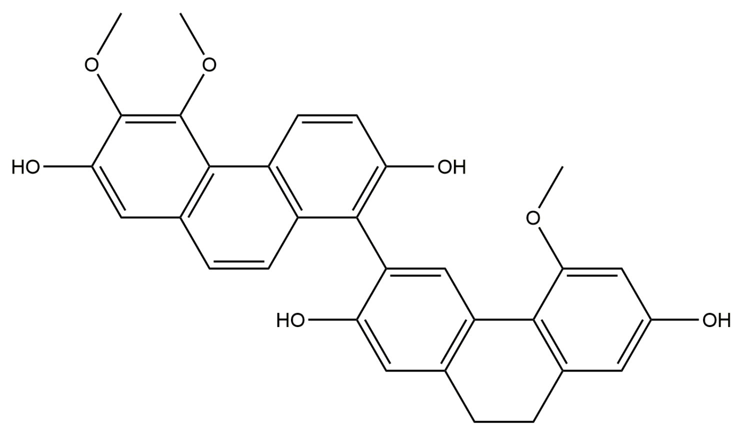
26



27



28

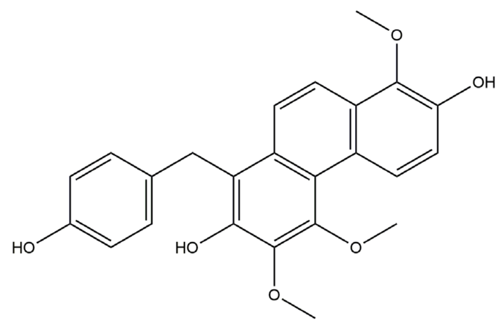


29

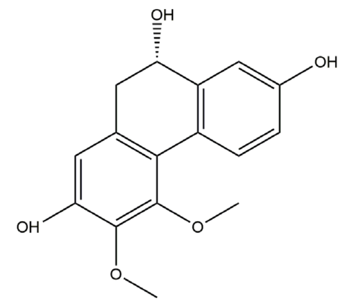
PHENANTHRENES

Phenanthrenes are some of the secondary metabolites most often found in native orchids from the most diverse regions of the planet (Kovács et al. 2008, Toth et al. 2017). They are metabolites produced biosynthetically from the oxidative coupling of stilbenes. They can be found with several structural variants, such as reduced positions (especially between the C9-C10 carbons), methylations, hydroxylations, oxidations to quinone rings, and even in the form of dimers and trimers (Kovács et al. 2008). In this review, it was found that species of American orchids belonging to taxonomically distinct subtribes (Oncidiinae, Maxilariinae, Laeliinae and Cyrtopodiinae) produce phenanthrenes. Phenanthrenes in plants are known to be phytoalexins that are able to inhibit the growth of pathogenic fungi.

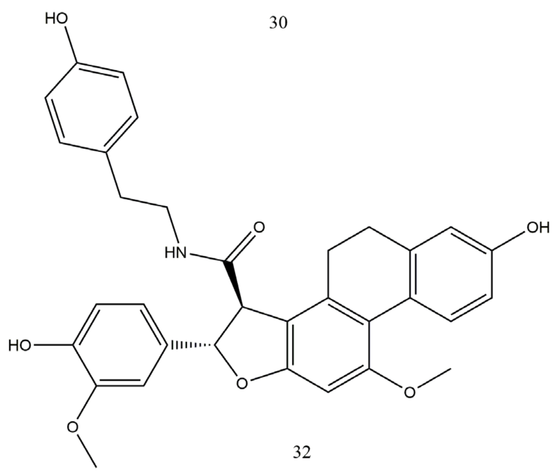
The phenanthrene moscatin was isolated from the Amazonian orchid *Oncidium baueri* (**13**). In their study, the authors showed that moscatin has moderate antiproliferative activity against several lines of human cancer cells, with emphasis on 786-0 kidney cancer cells with GI_{50} 25.5 $\mu g.mL^{-1}$. However, this compound showed antiproliferative activity against healthy human keratinocyte HaCat cells in similar concentration (Monteiro et al. 2014).



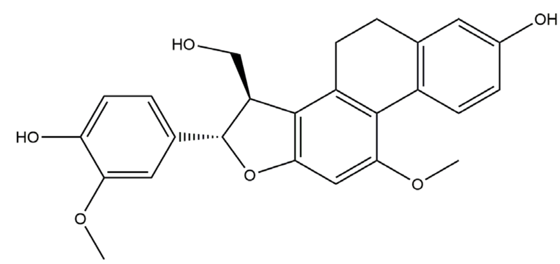
30



31



32



33

The species of Caribbean orchid, *Oncidium cebolleta*, is used in local folk medicine in the form of a paste as a remedy for pain and inflammation in muscle contusions. The chemical study of this orchid revealed the presence of 13 compounds of the class of phenanthrenoids, highlighting the highly oxygenated dihydro-phenanthrene (**14**) and a 1,4-phenanthrenequinone (**15**) (Stermitz et al. 1983). A cytotoxic phenanthrenequinone was also isolated in the species *Cattleya tigrina* from southern Brazil (Ferreira et al. 2021).

Phenanthrenes, 9,10-dihydrophenanthrenes and a previously unknown phenanthrene-1,4-dione, 9,10-dihydro-5-hydroxy-2-methoxyphenanthrene-1,4-dione **16** were isolated from the species *Oncidium isthmi*, native to central America. This compound proved to be active against NCI H-460 lung cancer cells with IC_{50} 5.0 μM, inducing apoptosis (Williams et al. 2012). In the same study, methoxylated phenanthrenes (**18**-**19**) were also isolated from *Oncidium microchillum*, including the di-methoxylated compound (**19**) in positions 9 and 10 (Nainwal et al.2019).

The species *Gomesa recurva*, also from the subtribe Oncidiinae, was studied phytochemically, identifying four phenanthrenes. Phenanthrene compound **19** showed activity against HeLa and Vero cells with IC_{50} 36.5 and 24.0 μg.mL^{-1} respectively (Savaris et al. 2018).

The phenanthrene 9,10-dihydro-4-methoxy phenanthren-2,7-diol (**20**) was isolated from *Laelia marginata* (=*Schomburgkia crispa*), a species closely related to genus *Myrmecophila*, and showed antiproliferative activity against HPV-modified HeLa and SiHa cancer cells (CC_{50} 5.86 ± 0.19 and 20.78 ± 2.72 μg.mL^{-1} respectively) (Belloto et al. 2018). Phenanthrenes and dihydrophenanthrenes have also been isolated from the species *Myrmecophilla humboltii* (Williams et al. 2012).

A chemical study of the orchid *Laelia anceps* led to the identification of 2,7-dihydroxy-3,4,9-trimethoxyphenantrene (**21**). The plant is used in traditional Mexican medicine as an infusion to reduce postpartum pain. In their study, the authors evaluated the antihypertensive potential of the plant extract and of compound **21**, showing that they induce relaxation in the aortic rings of rats via an endothelium-independent pathway (Vergara-Galicia et al. 2010a, Vergara-Galicia et al. 2010b).

Maxillaria densa was selected as part of an extensive research program on native Mexican species with spasmolytic activity. Initial studies led to the isolation of several phenanthrenes, and the structures of previously unknown phenanthrenes being elucidated in the study using X-ray diffraction (Estrada et al. 1999). The phenanthrenes 2,5-dihydroxy-3,4-dimethoxyphenanthrene (**22**), fimbriol-A (**23**), and nudol (**24**), isolated from *M. densa* provoked the concentration-dependent inhibition of spontaneous contractions of the rat ileum (Estrada et al. 2004). In another study, phenanthrenes from *M. densa* were found to induce a significant concentration-dependent and endothelium-independent relaxant effect on aorta rings precontracted with norepinephrine (Rendón-Vallejo et al. 2012). The most-active compound (**21**), also found in *Laelia anceps*, proved to be capable of inhibiting chemically induced contractility.

The phenanthrene 4,7-dihydroxy-2-methoxy-9,10-dihydrophenanthrene (**25**) was identified from the species *Encyclia longifolia* (Bhattacharyya et al. 2006). A symmetric dimeric diphenanthrene (**26**) was isolated from *Prosthechea michuacana* (synonym *Encyclia michuacana*), which contains an unusual prenylation, unique among New World orchids, and which has shown potent antioxidant activity (Gutierrez 2010).

There are reports of studies of secondary metabolites from two species of orchids from the subtribe *Cyrtopodiinae*. Species of genus *Cyrtopodium* are used in American folk medicine to treat muscular lesions and inflammatory processes. *Cyrtopodium macrobulbon* is an orchid used in traditional Mexican medicine as an analgesic and anti-inflammatory of the urinary tract. Pharmacological studies have shown that the extract of this species is not toxic to mice (LD_{50} > 5000 $mg.kg^{-1}$). Antinociceptive biological activity has been attributed to the presence of stilbenes (below). However, in their study, the authors identified phenanthrenes and 9,10-dihydrophenanthrene, and proposed the use of the phenanthrene ephemeranthol B 27 as a marker for this species of orchid, used in the standardisation and quality control of medicinal preparations based on the plant, given its molecular stability and ease of HPLC analysis (Morales-Sánchez et al. 2014).

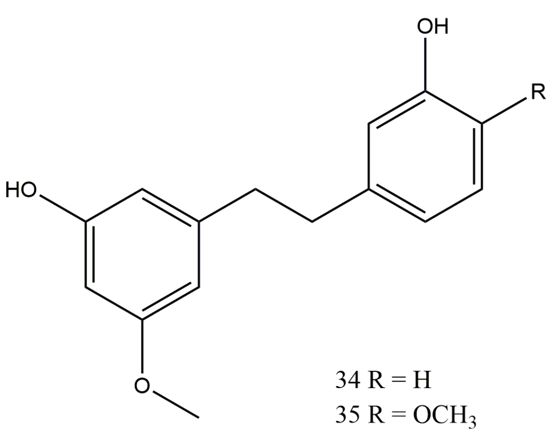
A recent chemical study of the roots of the species *Cyrtopodium paniculatum*, native to Colombia, resulted in the identification of several new phenanthrenes (Auberon et al. 2017); dihydrophenanthrenes, phenanthrenes, phenanthrenequinones and even rare phenanthrene dimers were also identified. Standing out on this broad list of isolated phenanthrenes and bi-phenanthrenes, are a highly oxygenated 1,4-phenanthrenequinone (**28**) and a bi-phenanthrene comprising a reduced portion and an unsaturated portion between carbons 9,10 and 9',10 (**29**), which showed low activity against U-87 human glioblastoma cells.

A study of the above-ground parts of the orchid *Cyrtopodium paniculatum* led to the isolation of several previously unknown phenanthrenes, dihydrophenanthrenes and one benzyl-phenanthrene **30**, in addition to many other phenanthrenes. This is the only report of benzyl-phenanthrenes occurring in neotropical orchids (Auberon et al. 2016), which proved to be a productive source of phenanthrenes with interesting structural variations. Also found was the presence of a phenanthrene nitrogen derivative (**31**), a 9,10-dihydro-phenanthrene hydroxylated on carbon sp^3 with a defined *S* absolute configuration (**32**), in addition to phenanthrene-furan derivatives (**33**).

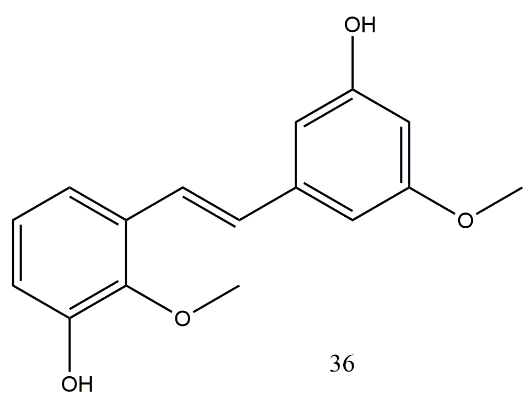
STILBENES

Stilbenes are a class of specialised metabolites that are not widely found in nature, but with a strong presence in Orchidaceae. Stilbenes have recently been gaining attention in pharmacological studies due to the great interest in the anti-cancer activity of combretastatins, isolated from the African bushwillow *Combretum caffrum* (Combretaceae) (Nainwal et al. 2019). In neotropical orchids, the most frequent reports include species from the subtribes Laeliinae, Cyrtopodiinae, Oncidiinae, Maxilariinae and Cypripedioidea, sharing with the phenanthrenes the position of the specialised metabolites more common in neotropical orchids. Indeed, stilbenes are biosynthetic precursors of phenanthrenes, which are obtained through aromatic oxidative-coupling stilbene reactions. However, there tends to be a lower structural diversity among isolated stilbenes compared to the phenanthrenes. Despite being common, in most cases batatasin III (**34**), and gigantol (**35**) and their derivatives, such as the most common stilbenes, are found.

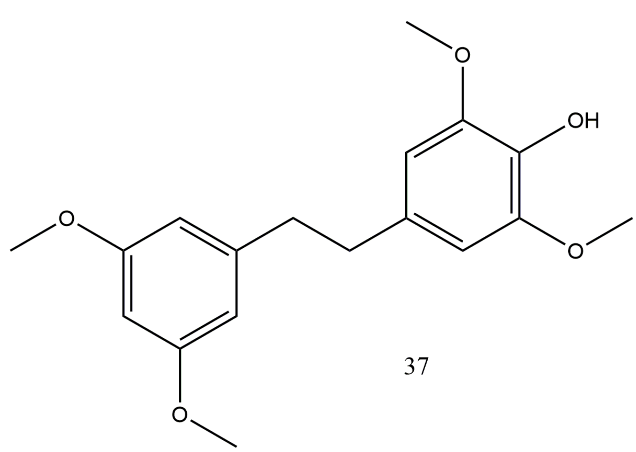
Gigantol and batatasin III are among the most-commonly isolated simple dihydro-stilbenes, as in the case of the species *Cyrtopodium macrobulbon* (Morales-Sánchez



34 R = H
35 R = OCH_3



36

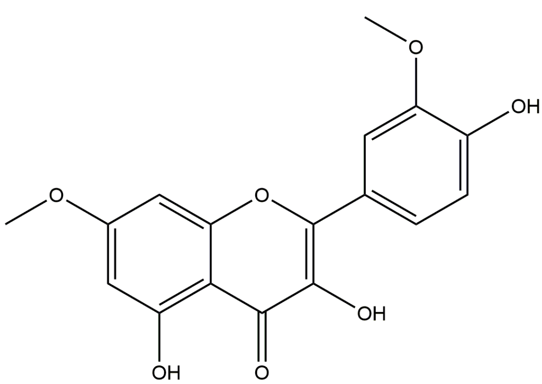


37

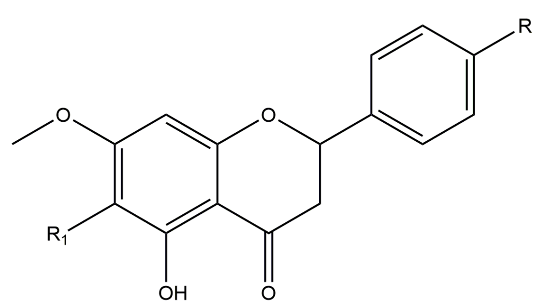
et al. 2014), *Cyrtopodium paniculatum* (Auberon et al, 2016), *Epidendrum rigidum* (Hernandez-Romero et al. 2005), *Laelia marginata* (Belloto et al. 2018) and *Oncidium baueri* (Monteiro et al. 2014), among various other species. In a study carried out with the species *Scaphyglottis rigida*, it was shown that purified gigantol has interesting antinociceptive activity (Déciga-Campos et al. 2007); the authors believe that this compound was responsible for similar activity seen in crude plant extracts. Batatasin III also shows interesting antiproliferative activity against human tumour cells (Monteiro et al. 2014). Important among the alpha-alpha' unsaturated stilbenes is phoyunbene C (**36**), isolated from *Maxillaria picta* (Almeida et al. 2014), which showed cytotoxic activity against the cell lines HepG2 and FHCC-98 (Wang et al. 2012). Recently, an in-depth study on the induction of apoptosis in tumour cells was carried out with stilbenes isolated from hybrids of the species *Oncidium isthmi* and *Myrmecophylla humboldtti*, and the commercial hybrid *Oncidium* Sharry Baby (Williams et al. 2012). In this study, in addition to batatasin III, the authors isolated the previously unknown dihydrostilbene 4-(3,5-dimethoxyphenethyl)-2,6-dimethoxyphenol (**37**), which was shown to induce apoptosis in human tumour cells.

FLAVONOIDS

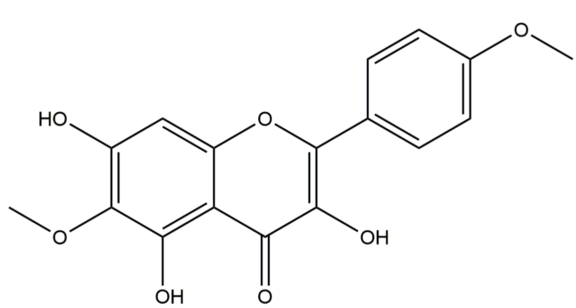
Flavonoids have rarely been reported in chemical studies of native orchids from Asia and Europe. On the other hand, the few studies with neotropical species have demonstrated a significant presence of these metabolites, especially in plants from the subtribes *Laeliinae* and *Oncidiinae*. This continental chemical distinction has recently been discussed (Savaris



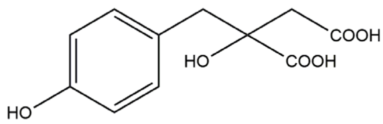
38



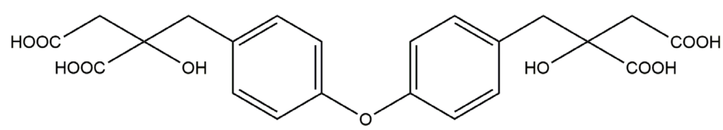
39 R = OH; R_1 = Apiose-glucose (3->1)
40 R = OCH_3; R_1 = Apiose-glucose (3->1)



41



42



43

et al. 2018). The flavonoid rhamnazin (38), which has anti-cancer activity, was isolated from the species *Laelia marginata*. As a significant result, two new flavanones were discovered, obtained in small quantities from the species of Amazonian orchid *Oncidium baueri*, both from the leaves and pseudobulbs (Monteiro et al. 2014), and from the flowers (Ferreira et al. 2019). These flavonoids, given the name onciabauerins A and B (**39**, **40**), show a unique binding pattern between glucose and apiose units via the carbon 3 of the glucose. Large amounts of known glycosylated flavonoids have been isolated from the same species of orchid. Species of genus *Oncidium* native to central America have also been reported to produce flavonoids.

The flavone hortensin (**41**), was identified from the South American species *Miltonia flavescens*. This compound demonstrated interesting biological activity against multidrug-resistant human ovarian sarcoma cells (NCI-ADR/RES), and lesser activity against human ovarian carcinoma (OVCAR) and non-cancerous epithelial cells (HaCat) (Porte et al. 2014).

MALIC ACID DERIVATIVES

Derivatives of eucomic acid (**42**), itself a derivative of malic acid, have frequently been reported both in native species from Asia, Europe and Africa, and less commonly in neotropical species. The crispoic acid (**43**), a dimer of eucomic acid, was discovered in chemical studies of the species *Laelia marginata*, which produces it in large amounts. This compound showed no anti-cancer or antiviral biological activity. Native terrestrial species of genus *Habenaria* from North America produce eucomic acid, as well as other malic acid derivatives like habenariol and its glucosilated derivative, haberianoside, known for their feeding deterrent activities (Wilson et al. 1999. Johnson et al. 1999). It is believed that eucomic acid may be involved in processes that control plant growth (Belloto et al. 2018).

CONCLUSIONS

The present study is the first review of the chemical and biological potential of native orchids from the Americas and the Caribbean. Despite the small number of species studied under these aspects to date, in contrast to the large number of species distributed across the continent, it appears that orchids may be an interesting source of molecules from the classes of phenanthrenes and stilbenes, especially since many show interesting biological anti-cancer activity. The use of orchids by traditional populations against inflammatory diseases in the Americas may be an important indication for future bio-guided studies of bioactive metabolites. It is therefore believed that better understanding of the potential of these plants can help to stimulate the comprehensive study of a greater number of species, thereby helping to encourage works of environmental preservation and recognise these plants as a potential source of pharmacologically important compounds.

Acknowledgments

The authors would like to thank the Fundação Araucária (Napi Biodiversidade: Recursos Genéticos e Biotecnologia), Coordenação de Aperfeiçoamento de

Pessoal de Nível Superior (Capes) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for the financial support given to various research projects.

REFERENCES

ALMEIDA TL ET AL. 2014. Chemical study and antiproliferative, trypanocidal and leishmanicidal activities of *Maxillaria picta*. Quim Nova 37(7): 1151-1157.

AUBERON F, OLANTUJI OP, HERBETTE G, RAMINOSON D, ANTHEAUME C, SOENGAS B, BONTÉ F & LOBSTEIN A. 2016. Chemical constituents from the aerial parts of *Cyrtopodium paniculatum*. Molecules 21(10): 1418.

AUBERON F, OLANTUJI OP, RAMINOSON D, MULLER CD, SOENGAS B, BONTÉ F & LOBSTEIN A. 2017. Isolation of novel stilbenoids from the roots of *Cyrtopodium paniculatum* (Orchidaceae). Fitoterapia 116: 99-105.

ARAUJO-LIMA CF, FELZENSZWALB I & MACEDO AF. 2021. *Cyrtopodium glutiniferum*, an example of orchid used in folk medicine: phytochemical and biological aspects. In: Merillon JM & Kodja H (Eds), Orchids Phytochemistry, Biology and Horticulture. Reference Series in Phytochemistry. Springer, Cham.

ASSELEIH LMC, GARCÍA RAM & CRUZ J. 2015. Ethnobotany, pharmacology and chemistry of medicinal orchids from Veracruz. J Agric Sci Tech 5: 745-754.

BARRAGÁN-ZARATE GS, LAGUNEZ-RIVERA L, SOLANO R, PINEDA-PENA EA, LANDA-JUARÉZ AY, CHÁVEZ-PINA AE, CARRANZA-ALVAREZ C & HERNÁNDEZ-BENAVIDES DM. 2020. *Prosthechea karwinskii*, an orchid used as traditional medicine, exerts anti-inflammatory activity and inhibits ROS. J Enthopharmacol 253: 112632.

BARRETO DW & PARENTE JP. 2006. Chemical properties and biological activity of a polysaccharide from *Cyrtopodium cardiochilum*. Carbohydr Polym 64: 287-291.

BELLOTO AC ET AL. 2018. Crispoic acid, a new compound from *Laelia marginata* (Orchidaceae), and biological evaluations against parasites, human cancer cell lines and Zika virus. Nat Prod Res 32: 2916-2921.

BHATTACHARYYA J, PIRES MFO, FELIX LP, SILVA TMS & MAJETICH GF. 2006. Isolation and characterization of the 'flavonoid crystals' of three species of *Prosthechea*: Chemotaxonomic considerations of the genera *Prosthechea* and *Encyclia*. Nat Prod Com 2(7): 755-758.

BOND MO, AREGULLIN MA & LAUX MT. 2014. Antimicrobial, cytotoxic, and antiproliferative properties of native and invasive orchids in the Dominican ethnobotany. Pennscience J 12: 23-28.

BORBA EL, TRIGO JR & SEMIR J. 2001. Variation of diastereoisomeric pyrrolizidine alkaloids in *Pleurothallis* (Orchidaceae). Biochem System Ecol 29: 45-52.

CARRERA GC, BENEDITO EF, SOUZA LEAL T, PEDROSO DE MORAES C & GASPI FOG. 2014. Testes fitoquímicos em extratos foliares de *Oeceoclades maculata* Lindl. (Orchidaceae). Rev Bras Plantas Med 16: 938-944.

CASTLE L. 1886. Orchids: their structure, history and culture (illustrated). London: Fleet Street.

CHASE MW, CAMERON KM, FREUDENSTEIN JV, PRIDGEON AM, SALAZAR G, VAN DEN BERG C & SCHUITEMAN A. 2015. An updated classification of Orchidaceae. Botan J Linnean Soc 177: 151-174.

COTA BB, MAGALHÃES A, PIMENTA AMC, SIQUEIRA EP, ALVES TMA & ZANI CL. 2008. Chemical constituents of *Habenaria petalodes* Lindl. (Orchidaceae). J Braz Chem Soc 19: 1098-1104.

COURTNEY MS, RUSSELL BW, VANESSA LN, JULIE AL, O'NEIL JOHNSON M & GARY RE. 2012. Phenylpropanoids from *Phragmipedium calurum* and their antiproliferative activity. Phytochemistry 82: 172-175.

CRUZ-GARCIA G, GOMEZ RS & RIVERA LL. 2014. Documentation of the medicinal knowledge of *Prosthechea karwinskii* in a Mixtec community in Mexico. Rev Bras Farmacogn 24: 153-158.

DECIGA-CAMPOS M, PALACIOS ESPINOSA JF, REYES RAMIREZ A & MATA R. 2007. Antinociceptive and anti-inflammatory effects of compounds isolated from *Scaphyglottis livida* and *Maxillaria densa*. J Ethnopharmacol 114(2): 161-168.

DÍAZ-AVILÉS JN, MENDEZ JLA, MEDRANO NS, TAKETA ATC, FLORESCANO IAC & DÍAZ OJE. 2020. Phytochemical screening, antioxidant activity and toxicity of the orchids *Prosthechea cochleata* and *Prosthechea livida*-A preliminary study. J Med Herbs Ethnom 6: 117-122.

DUGGAL SC. 1971. Orchids in human affairs (a review). Int J Crude Drug Res 11: 1727-1733.

ESTRADA S, ACEVEDO L, RODRIGUEZ M, TOSCANO RA & MATA R. 2002. New triterpenoids from the orchids *Scaphyglottis livida* and *Nidema boothii*. Nat Prod Lett 16(2): 81-86.

ESTRADA S, TOSCANO RA & MATA R. 1999. New phenanthrene derivatives from *Maxillaria densa*. J Nat Prod 62: 1175-1178.

ESTRADA S, LÓPEZ GUERRERO JJ, VILLALOBOS MR & MATA R. 2004. Spasmolytic stilbenoids from *Maxillaria densa*. Fitoterapia 75: 690-695.

FERREIRA NP, CHIAVELLI LUR, SAVARIS CR, OLIVEIRA SM, LUCCA DL, MILANEZE GUTIERRE MA, FARIA RT & POMINI AM. 2019. Chemical study of the flowers of the orchid *Oncidium baueri*

Lindley and their visiting bees *Trigona spinipes* Fabricius. Biochem System Ecol 86: 103918.

FERREIRA NP, LUCCA DL, DINIZ BV, NEGRI MFN, GUTIERRE MAM, DE OLIVEIRA SM & POMINI AM. 2021. Chemical, chemophenetic, and anticancer studies of *Cattleya tigrina.* Biochem Syst Ecol 97: 104303.

FLORIANI AEO, FERREIRA J, SANTOS ARS, DELLE MONACHE F, YUNES RA & CECHINEL FILHO V. 1998. Analgesic compounds from *Epidendrum mosenii* stems. Pharmazie 53(6): 426-427.

GARCIA GC, GOMEZ RS & RIVERA LL. 2014. Documentation of the medicinal knowledge of *Prosthechea karwinskii* in a Mixtec community in Mexico. Rev Bras Farmacogn 24: 153-158.

GARO E, HU JF, GOERING M, HOUGH G, O'NEIL JOHNSON M & ELDRIDGE G. 2007. Stilbenes from the orchid *Phragmipedium* sp. J Nat Prod70(6): 968-973.

GOVAERTS PB ET AL. 2018. World Checklist of Orchidaceae. Facilitated by the Royal Botanic Gardens, Kew.

GUTIERREZ RMP. 2010. Orchids: A review of uses in traditional medicine, its phytochemistry and pharmacology. J Med Plant Res 4(8): 592-638.

GUTIERREZ RMP. 2013. Evaluation of the hypoglycemic and hypolipidemic effects of triterpenoids from *Prosthechea michuacana* in streptozotocin-induced type 2 diabetic mice. Pharmacologia 4(3): 170-179.

GUTIERREZ RMP, NEIRA AM, BAEZ EG & DIAZ SL. 2010. Studies on the constituents of bulbs of the orchid *Prosthechea michuacana* and antioxidant activity. Chem Nat Comp 46(4): 554-561.

GUTIERREZ RMP, SOSA A, VADILLO H & VICTORIA TC. 2011. Effect of flavonoids from *Prosthechea michuacana* on carbon tetrachloride induced acute hepatotoxicity in mice. Pharm Biol 49(11): 1121-1127.

HABBU PV, SMITA DM, MAHADEVAN KM, SHASTRY R & BIRADAR SM. 2012. Protective effect of *Habenaria intermedia* tubers against acute and chronic physical and psychological stress paradigms in rats. Rev Bras Farmacogn 22: 568-579.

HERNÁNDEZ-ROMERO Y, ACEVEDO L, SANCHEZ M, SHIER WT, ABBAS HK & MATA R. 2005. Phytotoxic activity of bibenzyl derivatives from the orchid *Epidendrum rigidum*. J Agric Food Chem 53(16): 6276-6280.

HERNÁNDEZ-ROMERO Y, ROJAS JI, CASTILLO R, ROJAS A & MATA R. 2004. Spasmolytic effects, mode of action, and structure-activity relationships of stilbenoids from *Nidema boothii*. J Nat Prod 67(2): 160-167.

HOSSAIN MM. 2011. Therapeutic orchids: Traditional uses and recent advances - An overview. Fitoterapia 82: 102-140.

JOHNSON M K, ALEXANDER KE, LINDQUIST N & LOO G. 1999. A phenolic antioxidant from the freshwater orchid, *Habenaria repens*. Comp Biochem Physiol Part C Pharmacol Toxicol Endocrinol 122C(2): 211-214.

JYOTSHNA KHARE P & SHANKER K. 2016. Mangiferin: A review of sources and interventions for biological activities. BioFactors 42(5): 504-514. https: //doi.org/10.1002/biof.1308.

KOVACS A, VASAS A & HOHMANN J. 2008. Natural phenanthrenes and their biological activity. Phytochemistry 69(5): 1084-1110.

LINDSTRÖM B & LÜNNING B. 1971. Studies on orchidaceae alkaloids. 23. Alkaloids from *Liparis loeselii* (L.) L. C. Rich. and *Hammarbya paludosa* (L.) O. K. Acta Chem Scand 25(3): 895-897.

LINDSTRÖM B & LÜNNING B. 1972. Orchidaceae alkaloids. XXXV. Alkaloids from *Hammarbya paludosa* and *Liparis keitaoensis*. Acta Chem Scand 26(7): 2963-2965.

LUCCA DL ET AL. 2020. Biphenanthrene from *Stanhopea lietzei* (Orchidaceae) and its chemophenetic significance within neotropical species of the Cymbidieae tribe. Biochem System Ecol 89: 104014.

LUNNING B. 1964. Studies on Orchidaceae Alkaloids I. Screening of species for Alkaloids 1. Acta Chem Scand 18: 1507-1516.

MATA R, FIGUEROA M, GONZÁLEZ ANDRADE M, RIVERA CHÁVEZ JA, MADARIAGA MAZÓN A & DEL VALLE P. 2014. Calmodulin inhibitors from natural sources: An Update. J Nat Prod 78(3): 576-586.

MENON S & NAYEEM N. 2013. *Vanilla planifolia*: a review of a plant commonly used as flavouring agent. Int J Pharm Sci Rev Res 20(2): 225-228.

MILLER D & WARREN R. 1994. Orchids of the high mountain Atlantic rain forest in southeastern Brazil. Rio de Janeiro, Brazil, Salamandra.

MÓ E & IX WC. 2015. *Pleurothallis cardiothallis* (Plerothallidinae): An orchid withcontraceptive properties used by indigenous q'eqchi in Cobán, Alta Verapaz, Guatemala Alberta. Southern Albertta Ethnic Association 3(2): 15-16.

MONTEIRO JA ET AL. 2014. Oncibauerins A and B, new flavanones from *Oncidium baueri* (Orchidaceae). Phytochem Lett 9: 141-148.

MORALES-SANCHEZ V, RIVERO CRUZ I, LAGUNA HERNANDEZ G, SALAZAR CHAVEZ G & MATA R. 2014. Chemical composition, potential toxicity, and quality control procedures of the crude drug of *Cyrtopodium macrobulbon*. J Ethnopharm 154(3): 790-797.

NAINWAL LM, ALAM MM, SHAQUIQUZZAMAN M, MARELLA A & KAMAL A. 2019. Combretastatin-based compounds with therapeutic characteristics: a patent review. Expert Opin Ther Pat 29(9): 703-731. Epub 2019 Aug 8. PMID: 31369715.

NOVAES AP, ROSSI C, POFFO C, PRETTI JUNIOR E, OLIVEIRA AE, SCHLEMPER V, NIERO V, CECHINEL FILHO V & BURGER C. 2001. Preliminary evaluation of the hypoglicemic effect of some brazillian medicinal plants. Therapie 56: 427-430.

OLIVEIRA VB, YAMADA LT, FAGG CW & BRANDÃO MGL. 2012. Native foods from Brazilian biodiversity as a source of bioactive compounds. Food Res Int 48(1): 170-179.

OSSENBACH C. 2009. Orchids and orchidology in Central America. 500 years of history. Lankesteriana 9(1-2): 1-268.

PAPADOPULOS AST ET AL. 2013. Convergent evolution of floral signals underlies the success of Neotropical orchids. Proc Royal Soc B Biol Sci 280(1765): 20130.

PARENTE JP, ADAO CR, DA SILVA BP & TINOCO LW. 2014. Structural characterization of an acetylated glucomannan with antiinflammatory activity and gastroprotective property from *Cyrtopodium andersonii*. Carbohyd Res 391: 16-21.

PESQUISA FAPESP. 2018. Todas as plantas das Américas, por enquanto. Biodiversidade Botânica. Edition, 264 p.

PORTE LF, SANTIN SMO, CHIAVELLI LUR, SILVA CC, FARIA TJ, FARIA RT, RUIZ ALTG, CARVALHO JE & POMINI AM. 2014. Bioguided identification of antifungal and antiproliferative compounds from the Brazilian orchid *Miltonia flavescens* Lindl. Zeitschrift für Naturforschung C J Biosc 69(1-2): 46-52.

RAMÍREZ-GALICIA G, GARDUÑO-JUAREZ R, HEMMATEENEJAD B, DEEB O, ESTRADA SOTO S. 2007. QSAR Study on the relaxant agents from some mexican medicinal plants and synthetic related organic compounds. Chem. Biol. Drug Design. 70(2): 143-153.

RAMÍREZ SR, ELTZ T, FUJIWARA MK, GERLACH G, GOLDMAN-HUERTAS B, TSUTSUI ND & PIERCE NE. 2011. Asynchronous diversification in a specialized plant-pollinator mutualism. Science 333(6050): 1742-1746.

RAMÍREZ SR, GRAVENDEEL B, SINGER RB, MARSHALL CR & PIERCE NE. 2007. Dating the origin of the Orchidaceae from a fossil orchid with its pollinator. Nature 448: 1042-1045.

RENDON-VALLEJO P, HERNANDEZ-ABREU O, VERGARA-GALICIA J, MILLAN-PACHECO C, MEJIA A, IBARRA-BARAJAS M & ESTRADA-SOTO S. 2012. *Ex vivo* study of the vasorelaxant activity induced by phenanthrene derivatives isolated from *Maxillaria densa*. J Nat Prod 75(12): 2241-2245.

RIBEIRO MC, METZGER JP, MARTENSEN AC, PONZONI FJ & HIROTA MM. 2009. The Brazilian Atlantic Forest: how much is left, and how is the remaining forest distributed? Implications for conservation. Biol Conserv 142(6): 1141-1153.

ROSA PW, MACHADO MS, CAMPOS BUZZI F, NIERO R, DELLE MONACHE F & CECHINEL FILHO V. 2007. Seasonal and biological variations of *Epidendrum mosenii*: quantification of 24-methylenecycloartanol using gas chromatography. Nat Prod Res 21(11): 975-981.

ROSA PW, MACHADO MS, NIERO R, ZACCHINO S, GETTE MA, DELLE MONACHE F & CECHINEL FILHO V. 2008. Seasonal phytochemical variation and antifungal evaluation of different parts of *Epidendrum mosenii*. Nat Prod Commun 3(4): 535-538.

SAVARIS CR ET AL. 2018. Phytochemical and biological studies of *Gomesa recurva* R. Br. (Orchidaceae): chemotaxonomic significance of the presence of phenanthrenoids. Biochem System Ecol 80: 11-13.

SCHULTES RE. 1979. Indícios da riqueza etnofarmacológica do noroeste da Amazônia. Acta Amazon 9(1): 209-215.

SHANMUGAVALLI N, UMASHANKAR V & RAHEEM. 2009. Antimicrobial activity of *Vanilla planifolia*. Indian J Sci Technol 2(3): 37-40.

SIEVERS AF. 1930.The herb hunters guide. Misc. Publ. No. 77. USDA, Washington.

STARKS CM, WILLIAMS RB, NORMAN VL, LAWRENCE JA, O'NEIL JOHNSON M & ELDRIDGE GR. 2012. Phenylpropanoids from *Phragmipedium calurum* and their antiproliferative activity. Phytochemistry 82: 172-175.

STERMITZ FR, SUESS TR, SCHAUER CK, ANDERSON OP & BYE JR R. 1983. New and old phenanthrene derivatives from *Oncidium cebolleta*, a peyote-replacement plant. J Nat Prod 46(3): 417-423.

STOKSTAD E. 2015. Orchids' dazzling diversity explained. Science 349(6251): 914.

SUT S, MAGGI F & DALL'ACQUA S. 2017. Bioactive secondary metabolites from orchids (Orchidaceae). Chem Biodivers 14(11): 1700172.

TATSUZAWA F, SAITO N, YOKOI M, SHIGIHARA A & HONDA T. 1998. Acylated cyanidin glycosides in the orange-red flowers of *Sophronitis coccinea*. Phytochemistry 49(3): 869-874.

TATSUZAWA F, SAITO N, YUKAWA T, HONDA T, SHINODA K, KATO K, MIYOSHI K. 2014. Acylated cyanidin 3,7-diglucosides in the red-purple flowers of *Sophronitis wittigiana* (Orchidaceae). J Japan Soc Hortic Sci 83(1): 64-71.

TEOH ES. 2019. Usage of Medicinal Orchids by North American Indians. In: Orchids as Aphrodisiac, Medicine or Food, Springer, p. 173-194.

TOTH B, ANDREA V & HOHMANN J. 2017. Phenanthrenes: A promising group of plant secondary metabolites. J Nat Prod 81(3): 661-678.

TOVAR GIJON CE, HERNANDEZ CARLOS B, BURGUENO TAPIA, E, CEDILLO PORTUGAL E & JOSEPH NATHAN P. 2006. A new C-glycosylflavone from *Encyclia michuacana*. J Mol Struc 783(1-3): 96-100.

VERGARA-GALICIA J, AGUIRRE CRESPO F, CASTILLO ESPANA P, ARROYO MORA A, LOPEZ ESCAMILLA, AL, VILLALOBOS MOLINA RF & ESTRADA SOTO S. 2010a. Micropropagation and vasorelaxant activity of *Laelia autumnalis* (Orchidaceae). Nat Prod Res 24(2): 106-114.

VERGARA-GALICIA J, ORTIZ ANDRADE, R, CASTILLO ESPANA P, IBARRA BARAJAS M, GALLARDO ORTIZ I, VILLALOBOS MOLINA R & ESTRADA SOTO S. 2008. Antihypertensive and vasorelaxant activities of Laelia autumnalis are mainly through calcium channel blockade. Vascular Pharm 49(1): 26-31.

VERGARA-GALICIA J, ORTIZ ANDRADE R, RIVERA LEYVA J, CASTILLO ESPANA P, VILLALOBOS MOLINA, R, IBARRA BARAJAS M, GALLARDO ORTIZ I & ESTRADA SOTO S. 2010b. Vasorelaxant and antihypertensive effects of methanolic extract from roots of *Laelia anceps* are mediated by calcium-channel antagonism. Fitoterapia 81(5): 350-357.

WANG G, GUO X, CHEN H, LIN T, XU Y, CHEN Q, LIU J, ZENG J, ZHANG XK & YAO X. 2012. A resveratrol analog, phoyunbene B, induces G2/M cell cycle arrest and apoptosis in HepG2 liver cancer cells. Bioorg Med Chem Lett 22: 2114-2118.

WILLIAMS CA. 1979. The leaf flavonoids of the Orchidaceae. Phytochemistry 18: 803-813.

WILLIAMS CA, DE BRITO ALT, HARBORNE JB, EAGLES J & WATERMAN PG. 1994. Methylated C-glycosylflavones as taxonomic markers in orchids of the subtribe Ornithocephalinae. Phytochemistry 37(4): 1045-1053.

WILLIAMS RB ET AL. 2012. Isolation of Apoptosis-Inducing Stilbenoids from Four Members of the Orchidaceae Family. Natural Product Chemistry. Planta Med 78(2): 160-165.

WILLIAMS RB ET AL. 2021. Isolation of apoptosis-inducing stilbenoids from four members of the Orchidaceae family. Planta Med 78(2): 160-165.

WILSON DM, FENICAL W, HAY M, LINDQUIST N & BOLSER R. 1999. Habenariol, a freshwater feeding deterrent from the aquatic orchid *Habenaria repens* (Orchidaceae). Phytochemistry 50(8): 1333-1336.

WILSON MF. 2007. Medicinal plant fact sheet: *Cypripedium*: lady's slipper orchids. Virginia: Arlington.

ZHONG SJ, WANG L, WU HT, LAN R & QIN XY. 2019. *Coeloglossum viride* var. *bracteatum* extract improves learning and memory of chemically-induced aging mice through upregulating neurotrophins BDNF and FGF2 and sequestering neuroinflammation. J Funct Foods 57(6): 40-47.

How to cite

POMINI AM, SAHYUN SA, OLIVEIRA SM & FARIA RT. 2023. Bioactive natural products from orchids native to the Americas - A review. An Acad Bras Cienc 95: e20211488. DOI 10.1590/0001-3765202320211488.

Manuscript received on November 12, 2021;
accepted for publication on January 26, 2023

ARMANDO MATEUS POMINI[1]
https://orcid.org/0000-0001-5296-7895

SANDRA APARECIDA SAHYUN[2]
https://orcid.org/0000-0002-7154-5169

SILVANA MARIA DE OLIVEIRA[1]
https://orcid.org/0000-0002-4809-3205

RICARDO TADEU DE FARIA[2]
https://orcid.org/0000-0002-7595-1965

[1]State University of Maringá, Department of Chemistry, Colombo Avenue 5790, 87020-900 Maringá, PR, Brazil

[2]State University of Londrina, Department of Agronomy, Celso Garcia Road, Km 380, 86057-970 Londrina, PR, Brazil

Correspondence to: **Armando Mateus Pomini**
E-mail: ampomini@uem.br

Author Contributions

Armando M. Pomini was responsible for supervision (lead), conceptualization (lead), data curation (equal), investigation (equal), formal analysis, methodology (lead), writing-original draft (lead); Sandra A. Sayhun for data curation (equal), formal analysis, investigation (equal), visualization, writing-original draft; Silvana M. de Oliveira for writing-original draft, investigation; Ricardo T. de Faria for conceptualization, writing-original draft, formal analysis.