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A REVIEW OF TRADITIONAL USES, PHYTOCHEMICALS AND BIOACTIVITIES OF THE GENUS *HYPOESTES*

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Abstract

Background: Plants have been used as a folkloric source of medicinal agents since the beginning of mankind. The genus *Hypoestes* (family Acanthaceae) includes over 150 species. The ethno-pharmacological studies of the plant belonging to this genus indicated that they possess various bioactivities as cytotoxic, anti-leismanial, antimicrobial, antimalarial, antioxidant, and anti-trypanosomal. Furthermore, they have been utilized in different traditional medicines for treating various aliments as eye sores, breast, liver, heart, and skin diseases, respiratory infections, anemia, malaria, scabies, typhoid, hypertension, and gonorrhea. This review focuses on the traditional uses, chemical constituents, and bioactivities of *Hypoestes* species.
Methods: The information was acquired from a literature searching in electronic databases such as ScienceDirect, PubMed, Google-Scholar, SpringerLink, Scopus, and Wiley up to 2017 for publications on genus *Hypoestes*.
Results: The genus *Hypoestes* had varied classes of chemical constituents, including diterpenoids, alkaloids, lignans, and pentacyclic triterpenes. Herein, 46 metabolites and more than 30 references have been cited.
Conclusion: This works provides a background for the future studies on *Hypoestes* species, particularly the species, which have not been extensively explored for separation and characterization of bioactive constituents and pharmacological potentials.

Keywords: *Hypoestes*, Acanthaceae, Uses, Chemical constituents, Biological activities.

List of abbreviations: ATCC: American Type Culture Collection; B16: Mouse melanoma; CAM: Chick chorioallantoic membrane; CCl_4: Carbon tetrachloride; B16F1: Mouse melanoma cells; CA46: Human Burkitt lymphoma; Conc: Concentration; CCRF-CEM: Drug sensitive T-lymphoblastoid; CEM/ADR5000: Multidrug-resistant T-lymphoblastoid; DNA: Deoxyribonucleic acid; ED_{50}: Effective dose; 5-FU: 5-fluorouracil; GOT: Glutamyl oxalacetate transaminases; GPT: Glutamate pyruvate transaminase; HEB4: Human normal melanocyte; HELA: cervical epitheloid carcinoma; HEPG2: Hepatocellular carcinoma; IC_{50}:The half maximal inhibitory concentration; IKK: kappa-B kinase subunit alpha; IZD: Inhibition zone diameter; IL: Interleukin; ILS: Increase in life spans; KB: Human epidermoid carcinoma cell; KCl: Potassium chloride; LPS: lipopolysaccharide; MCF_7: Human breast cancer; MIC: Minimum inhibitory concentration; MRC_5: Diploid human cell line; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; P-388: Murine lymphocytic leukemia: Leukemia; PCV: Packed cell volume; RBC: Red blood cells-Erythrocytes; RNA: Ribonucleic acid; RSA: Radical scavenging activity; SD_{90}: Suppressive dose 90; STM: Survival times mean; TLC: Thin layer chromatography.

Introduction

Plants have been used as a folkloric source of medicinal agents since the beginning of mankind. Despite major scientific progress in chemistry, drugs derived from plants still make an enormous contribution to drug discovery today and continue to be an important source to fight serious diseases as cancer, inflammation and bacterial and viral infections, especially in the developing countries (Zhang, 2004). Acanthaceae family is a tropical family consisting of ≈ two hundreds fifty genera and two thousands five hundreds species all over the world (Scotland and Vollesen, 2000). It is found in subtropical and tropical regions as Africa, Indo-Malaysia, Central America, and Brazil. It includes mainly perennial and annual herbs, climbers, and shrubs, as well as large trees. *Hypoestes* Soland. Ex R. Br. is one of the most important genera belonging to this family. Its generic name was attributed to both authors Robert Brown and Solander. *Hypoestes* is confined to the palaeotropics and subtropics, ranging from tropical Africa to Australia (Darbyshire, 2015).

The plants of this genus are present in Asia, Australia, East Indies, and Africa. This genus can be distinguished from other Acanthaceae`s genus by the inelastic bases of placenta and union of the monothecous anthers with resupinate corollas. It contains over 150 species, ≈40-100 of them are accepted (The Plantlist. 2013; Mabberley, 2008; Dyer, 1975) (Table 1).

Table 1: List of the accepted *Hypoestes* species (The Plant List, 2013)

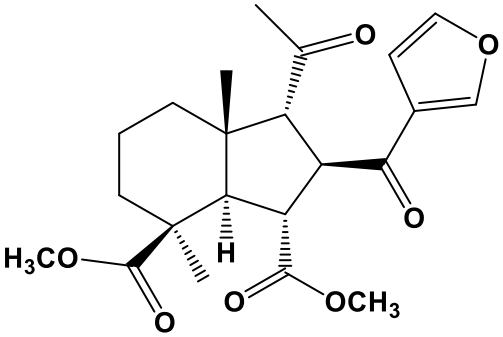
Species name	**Species name**	**Species name**
H. acuminata Baker	*H. fascicularis* Nees	*H. phyllostachya* Baker
H. angusta Benoist	*H. flavescens* Benoist	*H. poissonii* Benoist
H. angustilabiata Benoist	*H. flavovirens* Benoist	*H. potamophila* Heine
H. anisophylla Nees	*H. flexibilis* Nees	*H. pulchra* Nees
H. arachnopus Benoist	*H. forsskaolii* (Vahl) R.Br.	*H. purpurea* (L.) R. Br.
H. aristata (Vahl) Roem. & Schult.	*H. glandulifera* Scott-Elliot	*H. richardii* Nees
H. axillaris Benoist	*H. glandulosa* (S. Moore) Benoist	*H. rodriguesiana* Balf.f.
H. bakeri Vatke	*H. gracilis* Nees	*H. saboureaui* Benoist
H. barteri T. Anderson	*H. hastata* Benoist	*H. sanguinolenta* (Van Houtte) Hook. f.
H. betsiliensis S. Moore	*H. hirsuta* Nees	*H. saxicola* Nees
H. bodinieri H. Lév.	*H. humbertii* Benoist	*H. scoparia* Benoist
H. bojeriana Nees	*H. humifusa* Benoist	*H. secundiflora* Baker
H. bosseri Benoist	*H. incompta* Scott-Elliot	*H. serpens* R.Br.
H. brachiata Baker	*H. inconspicua* Balf.f.	*H. sessilifolia* Baker
H. calycina Benoist	*H. isalensis* Benoist	*H. setigera* Benoist
H. cancellata Nees	*H. jasminoides* Baker	*H. spicata* Nees
H. capitata Benoist	*H. juanensis* Benoist	*H. stachyoides* Baker
H. catatii Benoist	*H. laeta* Benoist	*H. stenoptera* Benoist
H. caudata Benoist	*H. lasioclada* Nees	*H. taeniata* Benoist
H. cernua Nees	*H. lasiostegia* Nees	*H. tetraptera* Benoist
H. chloroclada Baker	*H. leptostegia* S. Moore	*H. teucrioides* Nees
H. chlorotricha (Bojer ex Nees) Benoist	*H. longilabiata* Scott-Elliot	*H. teysmanniana* Miq.
H. cinerascens Benoist	*H. longispica* Benoist	*H. thomsoniana* Nees
H. cochlearia Benoist	*H. longituba* Benoist	*H. transversa* Benoist
H. comorensis Baker	*H. loniceroides* Baker	*H. trichochlamys* Baker
H. comosa Benoist	*H. macilenta* Benoist	*H. triflora* (Forssk.) Roem. & Schult.
H. complanata Benoist	*H. maculosa* Nees	*H. tubiflora* Benoist
H. congestiflora Baker	*H. mangokiensis* Benoist	*H. unilateralis* Baker
H. consanguinea Lindau	*H. mollissima* (Vahl) Nees	*H. urophora* Benoist
H. corymbosa Baker	*H. multispicata* Benoist	*H. vagabunda* Benoist
H. cruenta Benoist	*H. neesiana* Kuntze	*H. verticillaris* (L.f.) Sol. ex Roem. & Schult.
H. cumingiana (Nees) Benth. & Hook. f.	*H. nummularifolia* Baker	*H. viguieri* Benoist
H. decaryana Benoist	*H. obtusifolia* Baker	*H. warpurioides* Benoist
H. diclipteroides Nees	*H. oppositiflora* Benoist	*H. phyllostachya* Baker
H. egena Benoist	*H. oxystegia* Nees	*H. poissonii* Benoist
H. elegans Nees	*H. parvula* Benoist	*H. potamophila* Heine
H. elliotii S. Moore	*H. perrieri* Benoist	*H. pulchra* Nees
H. erythrostachya Benoist		

Its species are distributed in various habitats: roadsides, woodland, dune and thick scrub, grassland, and forests. The taxonomical study of this genus has been carried out by Darbyshire et al. (2015). *Hypoestes aristata* Soland. ex Roem & Schult., *H. triflora* (Forssk.) Roem. & Schult., *H. aristata* (Vahl) Roem. & Schult., *H. verticillaris* (L.f.) Roem. & Schult., *H. serpens* (Vahl) R. Br., *H. forskaolii* (Vahl) R. Br., *Hypoestes rosea* P. Beauv, *Hypoestes purpurea* R. Br., *H. phyllostachya* "Rosea, and *Hypoestes pubescens* Balf.f are the commonly studied species of this genus. Members of this genus are commonly used in several countries traditional medicine all over the world for treating of various illness including, eye sores, breast, respiratory, skin, heart, and hepatic diseases, typhoid, anemia, gonorrhea, and malaria (Table 2).

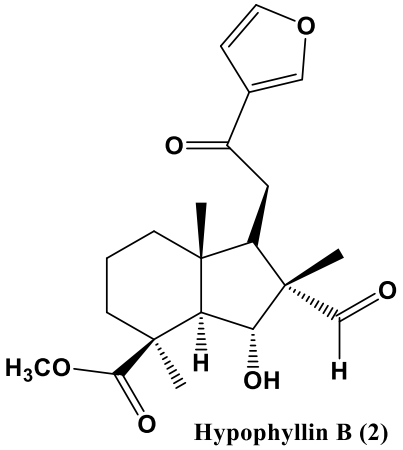
Table 2: List of some studied *Hypoestes* species and their traditional uses

Species	Traditional uses	Ref
Hypoestes aristata Soland. ex Roem and Schult. var. *aristata*	According to healers of the Xhosa tribe, the plant is used to treat complicated diseases like cancer, arthritis, tuberculosis, and bone fractures.	Bhat, 2014 Saeed et al. 2016
	It has been used against eye sores, breast diseases, respiratory infections, and malaria.	Saeed et al. 2016 Iwu, 1993
Hypoestes serpens (Vahl) R. Br.	In Malagasy folk medicine, it is used to treat high blood pressure and infectious vaginitis.	Rasoamiaranjanahary et al. 2003b
	In Madagascar and Saudi Arabia, it is used to treat heart disease and hypertension.	Wu et al. 2016
Hypoestes tiflora (Forskall Roemer et Schultes	In Rwanda, the leaves are used in native medicine to treat hepatic and skin diseases and worms.	Puyvelde et al. 1989; Mukazayire et al., 2011
	The juice of the leaves is also used by the Rwandese children as red ink.	
	In Bangladesh, leaf juice is orally administered for jaundice.	
	In Ethiopia, the leaves are used for anemia.	
Hypoestes forskalei Sol ex R.Br	In East African folk medicine, it is utilized for treating vomiting, headache, nausea, heartburn, and nightmare.	Al Musayeib et al., 2014
	In Cameroon, it used for skin infections (macerate whole plant and apply topically, twice a day)	Fongod et al. 2013
	In Ethiopia, it is used for babesia (crush whole plant, mix with honey and eat).	Teklay et al. 2013
	In Ethiopia, it is used for anthrax (crush whole part of *H. forskaolii* with the seeds of *Lepidium sativum*, and roots of *Solanum incanum*, macerate, filter and drink the fluid).	
	In Saudi and Yemeni traditional medicines: it is utilized for treating fungal skin diseases, scabies, and itching.	Mothana et al. 2009; 2014; 2011
	In Madagascar and Saudi Arabia, it is used to treat heart disease and hypertension.	Wu et al. 2016
	Among the Marakwet, it is used as a pesticide.	Kipkore et al. 2014
Hypoestes rosea P. Beauv	In Cameroon: it is used for typhoid (Infusion of plant (whole plant, leaves and stems), 1 glass, 4 times a day).	Fongod et al. 2013
	The dried leaves powder is used for the management of malaria by Nigerian natives.	Ojo-Amaize et al. 2007b
Hypoestes verticillaris (L.f.) Sol. ex Roem. & Schult.	In Kenya: it is used for treating tuberculosis, chest complaints, dry cough, pneumonia, and wound healing, also used as pesticide.	Kipkore *et al*. 2014
	In Madagascar and Saudi Arabia, it is used in treating hypertension and chest and heart diseases, gonorrhea, and cancer.	Al-Rehaily et al. 2002; Wu et al. 2016
Hypoestes purpurea R. Br.	In Taiwanese folk medicine, it is used as an anti-phlogistic, antipyretic, and liver protective agent.	Shen et al. 2004
Hypoestes pubescens Balf.f	It is utilized for treating fungal skin diseases and scabies	Mothana et al. 2009

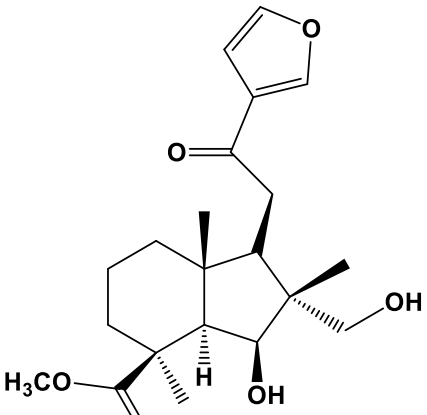
They possessed varied bioactivities as anti-inflammatory, antifungal, anti-leishmanial, antitumor, antibacterial, anti-trypanosomal, antimalarial, and vasorelaxant. Surveying the literatures revealed that no review available is on this genus regarding the chemical constituents and bioactivities. Hence, the main goal of this review is to highlight the traditional uses, various metabolites and their occurrence, and bioactivities reported for this genus species (Tables 3 & 4, Fig. 1-6). Also, it is aiming to supply knowledge to researchers for rapid identification of chemical constituents and pharmacological activities of *Hypoestes genus* plants. It can be utilized to validate the bioactivities and ethnomedicinal practices of this genus.



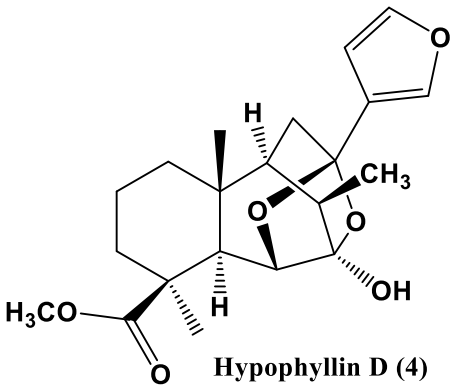
Hypophyllin A (1)



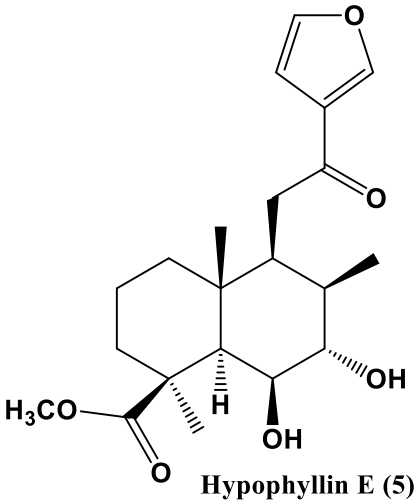
Hypophyllin B (2)



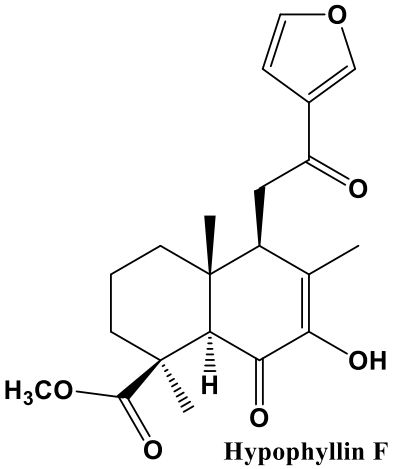
Hypophyllin C (3)



Hypophyllin D (4)

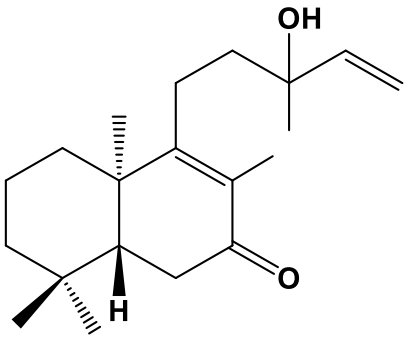


Hypophyllin E (5)

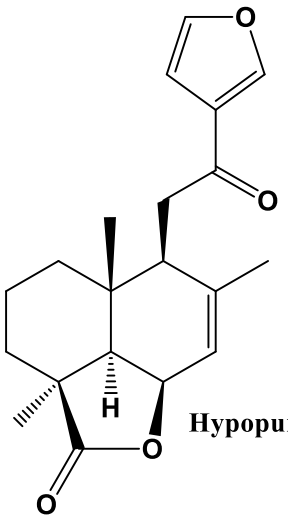


Hypophyllin F (6)

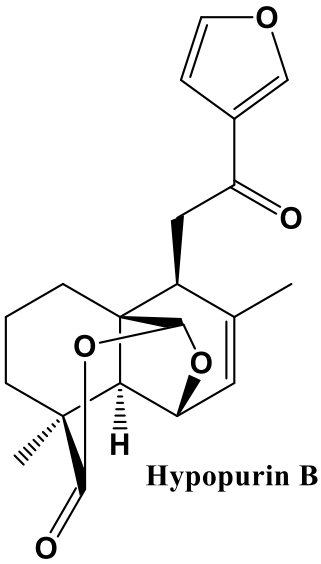
Figure 1: Chemical structures of compounds **1-6**



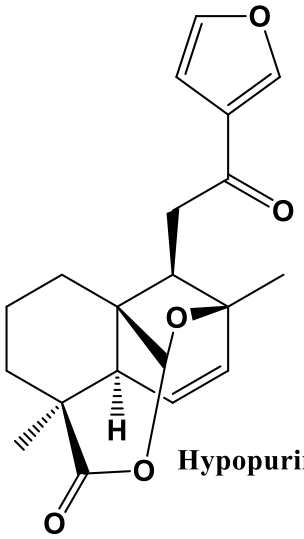
13-Hydroxy-7-oxo-labda-8-14-diene (7)



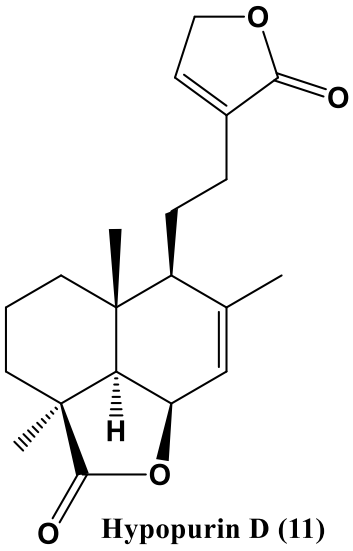
Hypopurin A (8)



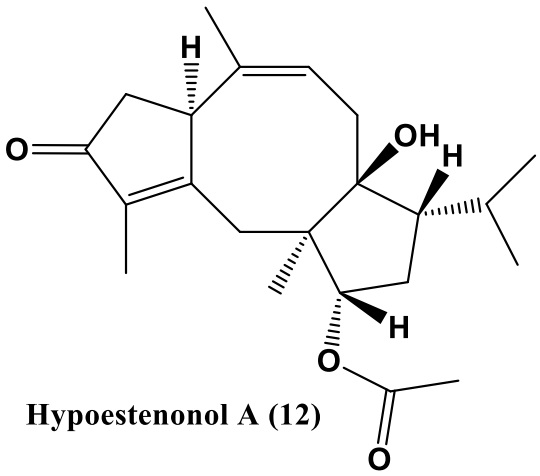
Hypopurin B (9)



Hypopurin C (10)



Hypopurin D (11)



Hypoestenonol A (12)

Figure 2: Chemical structures of compounds **7-12**

Table 3: List of compounds isolated from genus *Hypoestes*

Compound name	Source	Mol. Formula	Mol. Weight	Reference
Diterpenoids:				
A- Labdane-type:				
Hypophyllin A (**1**)	*H. phyllostachya* ``Rosea`` Baker J. Linn., whole plant	$C_{22}H_{28}O_7$	404	Wu et al., 2016
Hypophyllin B (**2**)	*H. phyllostachya* ``Rosea`` whole plant	$C_{21}H_{28}O_6$	376	Wu et al., 2016
Hypophyllin C (**3**)	*H. phyllostachya* ``Rosea``, whole plant	$C_{21}H_{30}O_6$	378	Wu et al., 2016
Hypophyllin D (**4**)	*H. phyllostachya* ``Rosea``, whole plant	$C_{21}H_{28}O_6$	376	Wu et al., 2016
Hypophyllin E (**5**)	*H. phyllostachya* ``Rosea``, whole plant	$C_{21}H_{30}O_6$	378	Wu et al., 2016
Hypophyllin F (**6**)	*H. phyllostachya* ``Rosea``, whole plant	$C_{21}H_{26}O_6$	374	Wu et al., 2016
13-Hydroxy-7-oxo-labda-8-14-diene (**7**)	*H. verticillaris*, aerial parts	$C_{20}H_{32}O_2$	304	Al-Rehaily et al., 2002
B- Furanolabdane-type:				
Hypopurin A (**8**)	*H. purpurea* (L.) R. Br. aerial parts	$C_{20}H_{24}O_4$	328	Shen et al., 2004
Hypopurin B (**9**)	*H. purpurea*, aerial parts	$C_{20}H_{22}O_5$	342	Shen et al., 2004
Hypopurin C (**10**)	*H. purpurea*, aerial parts	$C_{20}H_{22}O_5$	342	Shen et al., 2004
Hypopurin D (**11**)	*H. purpurea*, aerial parts	$C_{20}H_{26}O_4$	330	Shen et al., 2004
C- Fusicoccanes-type:				
Hypoestenonol A (**12**)	*H. forskalei*, (Vahl) Sol. ex Roem. & Schult., aerial parts	$C_{22}H_{32}O_4$	360	Al Musayeib et al., 2014
Hypoestenonol B (**13**)	*H. forskalei*, aerial parts	$C_{22}H_{32}O_4$	360	Al Musayeib et al., 2014
Verticillarone (**14**)	*H. forskalei*, aerial parts	$C_{20}H_{26}O_5$	346	Al Musayeib et al., 2014
	H. verticillaris (L. f.) Sol. ex Roem. & Schult., aerial parts			Al-Rehaily et al., 2002
Hypoestenone (**15**)	*H. forskalei*, aerial parts	$C_{20}H_{28}O_2$	300	Al Musayeib et al., 2014
	H. forskalei, aerial parts			Muhammad et al. 1997
Serpendione 1 (**16**)	*H. serpens*, (Vahl) R. Br., whole plant	$C_{21}H_{26}O_4$	342	Andriamihaja et al., 2001
Roseadione (**17**)	*H. rosea*, leaves and twigs	$C_{20}H_{30}O_3$	318	Adesomoju et al., 1983b
Deoxyhypoestenone (**18**)	*H. forskalei*, aerial parts	$C_{20}H_{30}O$	286	Muhammad et al. 1998
Dehydrohypoestenone (**19**)	*H. forskalei*, aerial parts	$C_{20}H_{26}O_2$	298	Muhammad et al. 1998
Hypoestene (**20**)	*H. forskalei*, aerial parts	$C_{21}H_{28}O_4$	344	Muhammad et al. 1998
Fusicoplagin D (**21**)	*H. forskalei*, aerial parts	$C_{22}H_{32}O_6$	392	Muhammad et al. 1998
(8)9-α-Epoxydeoxyhypoestenone (**22**)	*H. forskalei*, aerial parts	$C_{21}H_{30}O_2$	314	Muhammad et al. 1998
(8)9-α-Epoxyhypoestenone (**23**)	*H. forskalei*, aerial parts	$C_{20}H_{28}O_3$	316	Muhammad et al. 1998
Roseanolone (**24**)	*H. rosea* P. Beauv., whole plant	$C_{20}H_{30}O_3$	318	Okogun et al., 1982
Isoroseanolone (**25**)	*H. rosea* P. Beauv., whole plant	$C_{20}H_{34}O_3$	322	Okogun et al., 1982
Fusicoserpenol A (**26**)	*H. serpens*, leaves	$C_{20}H_{34}O_2$	306	Rasoamiaranjanahary et al., 2003b

D- Isopimarane type:				
7β-Hydroxyisopimara-8,15-dien-14-one (**27**)	*H. serpens*, leaves	$C_{20}H_{30}O_2$	302	Rasoamiaranjanahary et al., 2003a
14α-Hydroxyisopimara-7,15-dien-1-one (**28**)	*H. serpens*, leaves	$C_{20}H_{30}O_2$	302	Rasoamiaranjanahary et al., 2003a
1β,14α-Dihydroxyisopimara-7,15-diene (**29**)	*H. serpens*, leaves	$C_{20}H_{32}O_2$	304	Rasoamiaranjanahary et al., 2003a
7β-Acetoxyisopimara-8(14),15-dien-1-one (**30**)	*H. serpens*, leaves	$C_{21}H_{32}O_2$	316	Rasoamiaranjanahary et al., 2003a
7β-Hydroxyisopimara-8(14),15-dien-1-one (**31**)	*H. serpens*, leaves	$C_{20}H_{30}O_2$	302	Rasoamiaranjanahary et al., 2003a
E- Dolabellane type				
Dolabeserpenoic acid A (**32**)	*H. serpens*, leaves	$C_{20}H_{32}$	272	Rasoamiaranjanahary et al., 2003b
E- Verticillane-type				
Hypoestoxide (**33**)	*H. rosea*, leaves and twigs	$C_{22}H_{32}O_5$	376	Adesomoju et al., 1983a
Alkaloids				
Hypoestestatin 1 (**34**)	*H. verticillaris*, shrub	$C_{23}H_{27}NO_3$	365	Pettit et al., 1984
Hypoestestatin 2 (**35**)	*H. verticillaris*, shrub	$C_{23}H_{27}NO_4$	381	Pettit et al., 1984
Lignans				
α-O-methylcubebin (**36**)	*H. purpurea*, aerial parts	$C_{20}H_{20}O_6$	356	Shen et al., 2004
Hinoquinin (**37**)	*H. purpurea*, aerial parts	$C_{20}H_{18}O_6$	354	Shen et al., 2004
Helioxanthin (**38**)	*H. purpurea*, aerial parts	$C_{20}H_{12}O_6$	348	Shen et al., 2004
Justicidine E (**39**)	*H. purpurea*, aerial parts	$C_{20}H_{12}O_6$	348	Shen et al., 2004
Dehydroxycubebin (**40**)	*H. purpurea*, aerial parts	$C_{20}H_{20}O_5$	340	Shen et al., 2004
7-Hydroxyhinokinin (**41**)	*H. purpurea*, aerial parts	$C_{20}H_{18}O_8$	386	Shen et al., 2004
(-)-Hibalactone (**42**)	*H. purpurea*, aerial parts	$C_{20}H_{16}O_6$	352	Shen et al., 2004
(+)-Sesamin (**43**)	*H. forskalei*, aerial parts	$C_{20}H_{18}O_6$	354	Muhammad et al. 1997
Triterpenes				
Lupeol (**44**)	*H. purpurea*, aerial parts *H. rosea*, whole plant	$C_{30}H_{50}O$	426	Shen et al., 2004 Okogun et al., 1982
Betulin (**45**)	*H. purpurea*, aerial parts	$C_{30}H_{50}O_2$	442	Shen et al., 2004
Acids				
Benzoic acid (**46**)	*Hypoestes triflora*, leaves			Puyvelde et al., 1989

Phytochemical studies

Phytochemical investigations carried out on various *Hypoestes* species revealed the existence of different classes of phytochemicals, as diterpenoids (labdane-, furanolabadane-, fusicoccane-, isopimarane-, verticillane-, and dolabellane-types), alkaloids, lignans, and pentacyclic triterpenes (Table 3 and Fig. 1-6). This review gives an account about phytochemicals that have been separated from the genus. It would also assist further using of the plants of this genus. The list of the identified constituents and their chemical structures are depicted in table 3 and figures 1-6.

Biological activities

Hypoestes forskalei

Hypoestenonols A (**12**) and B (**13**), hypoestenone (**15**), and verticillarone (**14**) were isolated from the MeOH extract of the aerial parts of *Hypoestes forskalei*. The MeOH extract showed antimalarial potential against *Plasmodium falciparum* K 1-strain with half maximal inhibitory concentration (IC_{50}) 8.8 µg/mL, compared to chloroquine (IC_{50}) 0.3 µM). Also, it possessed antileishmanial effect towards *L. infantum* (half maximal inhibitory concentration IC_{50} 8.1 µg/mL) in comparison to fungizon (IC_{50} 1.5 µM). In addition, it exhibited anti-trypanosomal potential towards *T. cruzi* and *T. brucei* with IC_{50}s 9.1 and 8.1 µg/mL, respectively, compared to the positive controls benznidazol (IC_{50} 2.4 µM) and suramine (IC_{50} 0.03 µM), respectively without cytotoxicity (IC_{50} >64 µg/mL) on diploid human cell line (MRC_5)) in the fluorimetrical assay. A very weak *in vitro* antiplasmodial capacities were observed for hypoestenonol A (**12**) (IC_{50} 18.9 µM), verticillarone (**14**) (IC_{50} 25.1 µM), and hypoestenone (**15**) (IC_{50} 16.7 µM), in comparison to chloroquine (IC_{50} 0.3 µM) (Al Musayeib et al., 2014).

The cytotoxic activity of the MeOH extract of aerial parts of *H. forskalei* was determined using three human cancer cell lines: breast cancer (MCF7), hepatocellular carcinoma (HEPG2), and cervix cancer (HELA) cells. In

addition, the human normal melanocyte (HFB4) was used as normal nonmalignant cell, using sulforhodamine B colorimetric assay. The total MeOH extract showed cytotoxic activity against HFB4, HEPG2, and HELA with IC_{50}s 4.18, 29.9, and 16.3 μg/mL, respectively compared to doxorubicin (IC_{50}s 3.96, 4.90, and 3.63 μg/mL, respectively) and negative results against MCF7 cell line. However, the petroleum ether fraction possessed activity against MCF7, HFB4, HEPG2, and HELA with IC_{50}s 10.30, 20.30, 13.30, and 10.30 μg/mL, respectively compared to doxorubicin (IC_{50}s 4.50, 3.96, 4.90, and 3.63 μg/mL, respectively). The mother liquor also had moderate cytotoxic activity (IC_{50}s 15.80, 22.30, 20.60, and 12.10 μg/mL, respectively) towards the same cell lines. Moreover, the $CHCl_3$ and *n*-BuOH fractions exhibited more cytotoxic activity against the four cell lines with IC_{50}s 4.17, 5.18, 4.57, and 3.56 μg/mL, respectively for the $CHCl_3$ fraction and IC_{50}s 4.17, 5.59, 4.98, and 3.56 μg/mL, respectively for the *n*-BuOH fraction (Almehdar et al., 2012).

Table 4: List of the most potent compounds isolated from genus *Hypoestes*

Compound name	Biological activity	Assay, organism, or cell line	Biological results	Positive control	Reference
Hypophyllin A (**1**)	Vasorelaxant	KCl induced pre-contraction in rat aorta rings	9.04 maximum relaxant ratio (%) after 30 min	Nifedipine 91.67 maximum relaxant ratio (%) after 30 min	Wu et al., 2016
	Vasorelaxant		31.27 maximum relaxant ratio (%) after 1 h	Nifedipine 92.78 maximum relaxant ratio (%) after 1 h	Wu et al., 2016
Hypophyllin D (**4**)	Vasorelaxant	KCl induced pre-contraction in rat aorta rings	34.26 maximum relaxant ratio (%) after 30 min	Nifedipine 91.67 maximum relaxant ratio (%) after 30 min	Wu et al., 2016
	Vasorelaxant		64.28 maximum relaxant ratio (%) after 1 h	Nifedipine 92.78 maximum relaxant ratio (%) after 1 h	Wu et al., 2016
Hypophyllin E (**5**)	Vasorelaxant	KCl induced pre-contraction in rat aorta rings	36.80 maximum relaxant ratio (%) after 30 min	Nifedipine 91.67 maximum relaxant ratio (%) after 30 min	Wu et al., 2016
	Vasorelaxant		63.83 maximum relaxant ratio (%) after 1 h	Nifedipine 92.78 maximum relaxant ratio (%) after 1 h	Wu et al., 2016
Hypophyllin F (**6**)	Vasorelaxant	KCl induced pre-contraction in rat aorta rings	14.54 maximum relaxant ratio (%) after 30 min	Nifedipine 91.67 maximum relaxant ratio (%) after 30 min	Wu et al., 2016
			34.77 maximum relaxant ratio (%) after 1 h	Nifedipine 92.78 maximum relaxant ratio (%) after 1 h	Wu et al., 2016
Hypopurin A (**8**)	Cytotoxic	KB, MTT assay	9.4 μM (IC_{50})		Shen et al., 2004
Hypoestenonol A	Antimalarial	*P. falciparum*	18.9 μM	Chloroquine	Al Musayeib et

(**12**)		^{3}H-hypoxanthine incorporation assay	(IC_{50})	0.3 µM (IC_{50})	al., 2014
Verticillarone (**13**)	Antimalarial	*P. falciparum* ^{3}H-hypoxanthine incorporation assay	25.1 µM (IC_{50})	Chloroquine 0.3 µM (IC_{50})	Al Musayeib et al., 2014
Hypoestenone (**15**)	Antimalarial	*P. falciparum* ^{3}H-hypoxanthine incorporation assay	16.7 µM (IC_{50})	Chloroquine 0.3 µM (IC_{50})	Al Musayeib et al., 2014
Serpendione 1 (**16**)	Vasorelaxant	KCl induced pre-contraction in rat aorta rings	92.2 maxiumum relaxant ratio (%) after 30 min	Nifedipine 92.78 maxiumum relaxant ratio (%) after 1 h	Andriamihaja et al., 2001
Fusicoserpenol A (**26**)	Antifungal	TLC bioautographic assay Cladosporium Cucumerunum (ATCC No. 16402)	2.0 µg/TLC plate	Miconazole 1.0 µg/TLC plate	Rasoamiaranjanahary et al., 2003b
		Candida albicans	2.0 µg/TLC plate	Miconazole 1.0 µg/TLC plate	
7β-Hydroxyisopimara-8,15-dien-14-one (**27**)	Antifungal	*Cladosporium Cucumerunum* (ATCC No. 16402), TLC bioautographic assay	1.0 µg/TLC plate	Miconazole 1.0 µg/TLC plate	Rasoamiaranjanahary et al., 2003a
		Candida albicans, TLC bioautographic assay	1.0 µg/TLC plate	Miconazole 1.0 µg/TLC plate	
	Acetylcholinesterase inhibitory	TLC bioautographic assay	0.5 µg/TLC plate	Galanthamine 0.01 µg/TLC plate	
14α-Hydroxyisopimara-7,15-dien-1-one (**28**)	Antifungal	*Cladosporium Cucumerunum* (ATCC No. 16402), TLC bioautographic assay	1.0 < µg/TLC plate	Miconazole 1.0 µg/TLC plate	Rasoamiaranjanahary et al., 2003a
		Candida albicans, TLC bioautographic assay	1.0 < µg/TLC plate	Miconazole 1.0 µg/TLC plate	
	Acetylcholinesterase inhibitory	TLC bioautographic assay	0.2 µg/TLC plate	Galanthamine 0.01 µg/TLC plate	
7β-Acetoxyisopimara-8(14),15-dien-1-one (**30**)	Antifungal	*Cladosporium Cucumerunum* (ATCC No. 16402), TLC bioautographic assay	1.0 < µg/TLC plate	Miconazole 1.0 µg/TLC plate	Rasoamiaranjanahary et al., 2003a

		Candida albicans	1.0 < µg/TLC plate	Miconazole 1.0 µg/TLC plate	
Dolabeserpenoic acid A (**32**)	Antifungal	*Cladosporium Cucumerunum* (ATCC No. 16402), TLC bioautographic assay	5 µg/TLC plate	Miconazole 1.0 µg/TLC plate	Rasoamiaranjanahary et al., 2003a
		Candida albicans, TLC bioautographic assay	5 µg/TLC plate	Miconazole 1.0 µg/TLC plate	
Hypoestoxide (**33**)	Anti-inflammatory	Phorbol Ester-Induced Topical Inflammation	57 % thickness inhibition/ear	Dexamethasone-21-acetate 63 % thickness inhibition/ear	Ojo-Amaize et al., 2001
	Cytotoxic	B16F1 in ovo chick CAM assay	5.0 mg/kg-66% inhibition of lung colonization	rhIFN-α/β 100 units 55% inhibition of lung colonization	Ojo-Amaize et al., 2002
	Antimalarial	*P. falciparum* ^{3}H-hypoxanthine incorporation assay	10 µM (IC_{50})	Chloroquine 0.11 µM (IC_{50})	Ojo-Amaize et al., 2007b
Hypoestestatin 1 (**34**)	Cytotoxic	P-388 cells, MTT assay	10^{-5} µg/mL (ED_{50})		Pettit et al., 1984
Hypoestestatin 2 (**35**)	Cytotoxic	P-388 cells, MTT assay	10^{-5} µg/mL (ED_{50})		Pettit et al., 1984

Mothana et al. (2014) (2011) reported that the aerial parts of *H. forskalei* extract exhibited antiprotozoal activity towards *Leishmania infantum* with IC_{50} of 8.1 µg/mL compared to miltefosine (IC_{50} of 3.32 µg/mL). It displayed antimalarial potential IC_{50} (of 8.8 µg/mL) compared to chloroquine (IC_{50} of 0.3 µg/mL) towards chloroquine-sensitive *P. falciparum* K1-strain. It had anti-trypanosomal potential towards *T. brucei* Squib-427 strain (suramin-sensitive) with an IC_{50} 8.1 µg/mL, compared to suramin (IC_{50} 0.03 µg/mL) and against *T. cruzi* Tulahuen CL2 (benznidazole-sensitive) with an IC_{50} of 9.1 µg/mL, in comparison to beznidazole (IC_{50} 2.2 µg/mL). In addition, it had cytotoxic activity in resazurin fluorescent assay towards human lung fibroblast cell lines (MRC-5) with an IC_{50} 11.0 µg/mL, compared to tamoxifen (IC_{50} 11.0 µg/mL) (Mothana et al., 2011; 2014). *H. forskalei* aerial parts extract was assessed for cytotoxic, antimicrobial, and antioxidant activities. The antimicrobial effect was carried out towards *Staphylococcus aureus* (ATCC 6538), *Micrococcus flavus* (SBUG 16), *Bacillus subtilis* (ATCC 6059), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 11229), and *Candida maltosa* (SBUG) using agar diffusion and broth micro-dilution assays (Mothana et al., 2011). It possessed only antifungal potential (Conc. 4.0 mg/disc) towards *C. maltosa* with inhibition zone diameter (IZD) 18 mm, compared to amphotericin (Conc. 10 µg/disc, IZD 11 mm). Also, it had cytotoxic potential in microtiter plate assay towards human breast cancer (MCF-7) [ATCC HTB-22] and human urinary bladder carcinoma (5637) [ATCC HTB-9] cell lines with IC_{50}s 32.1 and 14.3 µg/mL, respectively compared to etoposide (IC_{50}s 5.62 and 2.27 µM, respectively). It showed potent concentration-dependent antioxidant potential with radical scavenging activity (RSA) 1.5, 14.8, 43.8, 96.5, and 94.7 % (conc. 10, 50, 100, 500, and 1000 µg/mL, respectively), in comparison to ascorbic acid (RSA: 45.2, 97.1, 96.5, 97.6, and 96.3%) at the same concentrations (Mothana et al., 2011). Muthaura et al. (2015) reported that MeOH of *H. forskalei* showed antimalarial activity against *P. falciparum* (D6 clone) with an IC_{50} 5.6 µg/mL in ^{3}H-hypoxanthine incorporation assay (Muthaura et al., 2015). Ubaha et al. (2012) reported that the leaves and stem H_2O extracts of *H. forskalei* possessed piscicidal potential towards *Clarias gariepinus* (African mud cat fish). The mortality diminished with reducing the extracts concentration at all treated fish's stages. The packed cell volume (PCV), concentration of hemoglobin, and count of red blood cells (RBC) of the treated fishes were noticeably decreased compared to the control. Thus, *H. forskalei* had high piscicidal and high toxic effects to the aquatic lives and could produce internal organs hazards on the fish consumers (Ubaha et al., 2012).

Hypoestes phyllostachya

Wu et al. (2016) evaluated the vasorelaxant effects on endothelium-intact thoracic aorta rings pre-contracted with potassium chloride (KCl) of hypophyllins A (**1**) and D-F (**4**-**6**) separated from aerial parts of *H. phyllostachya* (Wu et al., 2016). Hypophyllins A (**1**) and D-F (**4**-**6**) (Conc. 100 μM) exhibited potent vasorelaxant action with the maximum relaxant activity. Moreover, **4** and **5** showed a higher vasorelaxant effect than other compounds with the maximum relaxant ratios 64.28 and 63.83%, respectively compared to nifedipine (maximum relaxant ratio 92.78%). Whereas, **1** and **6** exhibited maximum relaxant values of 31.27 and 34.77%, respectively (Wu et al., 2016). Interestingly, **4** possessed an uncommon 8,9-dioxatricyclic[4.2.1.13,7]decane skeleton, indicating that this caged-moiety is possibly important for the vasorelaxant potential.

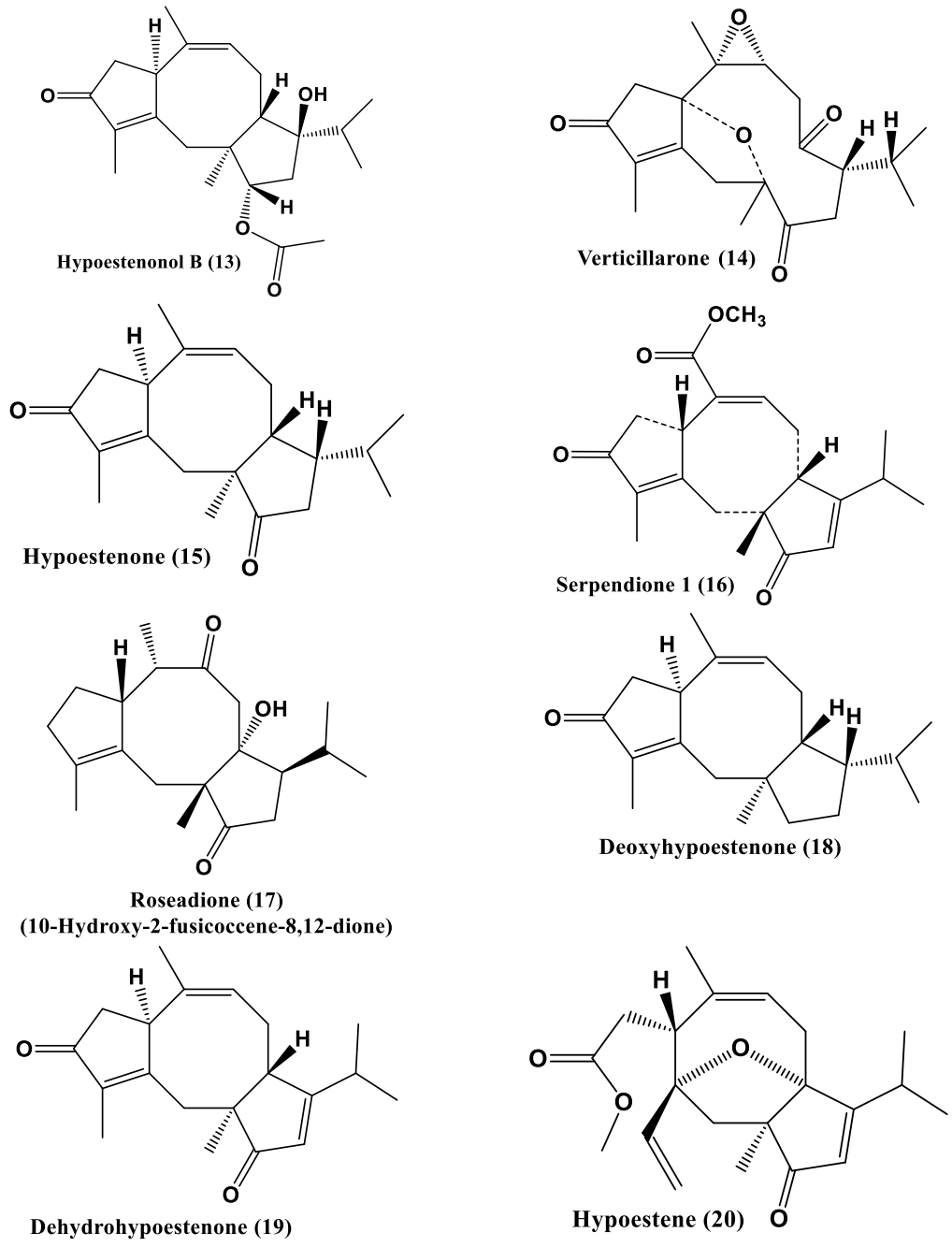


Figure 3: Chemical structures of compounds **13-20**

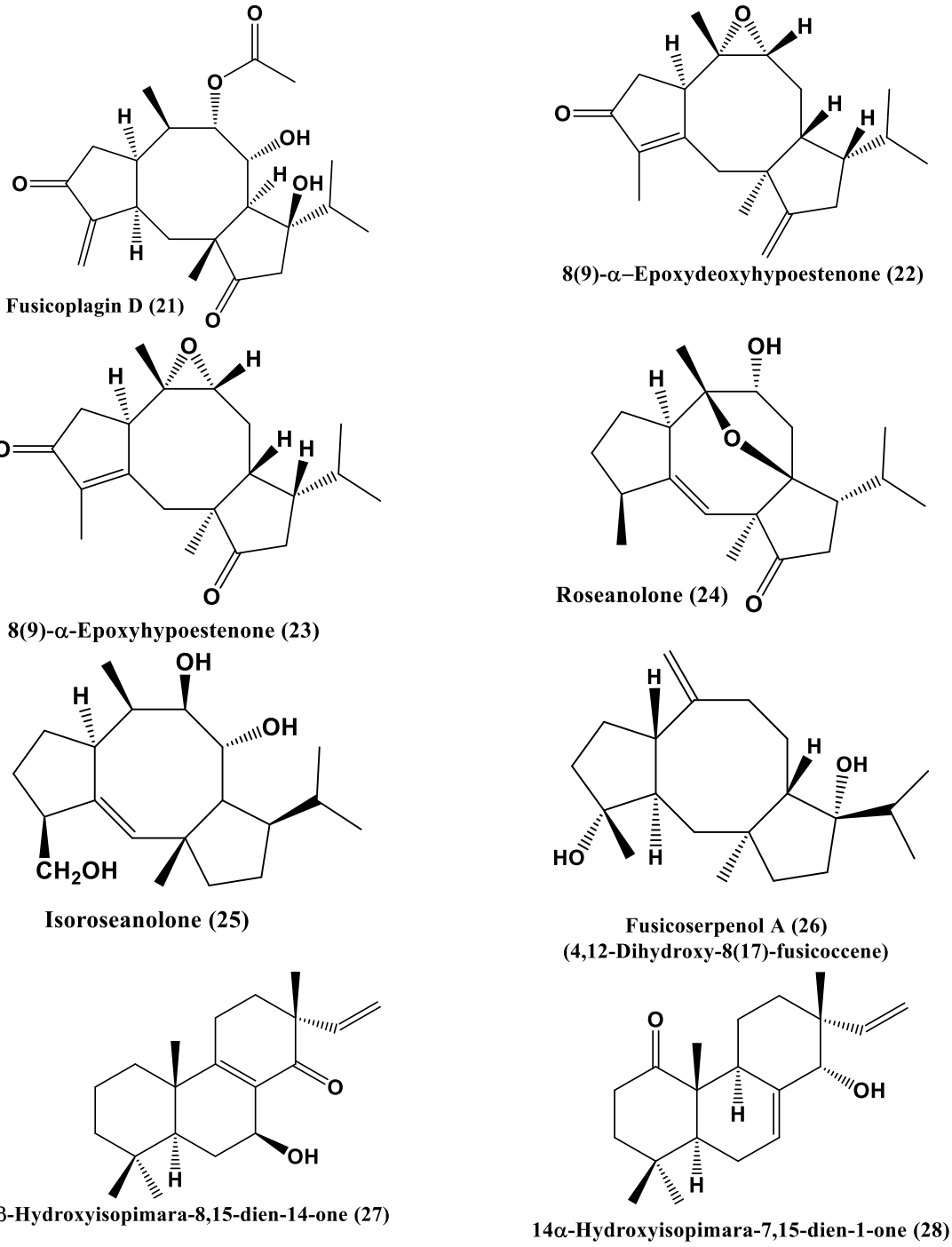


Figure 4: Chemical structures of compounds **21-28**

In addition, the presence of vicinal diol moiety as in **5** (two OH groups at C-7 and C-6) might also be critical to the vasorelaxant effect for the furanolabdane diterpenoids. The fascinating structures of hypophyllins will attract great interest for synthetic and biosynthetic communities. In addition, hypophyllins D (**4**) and E (**5**) also exhibited potent vasorelaxant activity, which made them promising lead compounds for the treatment of hypertension, heart disease, and stroke (Wu et al., 2016).

Hypoestes triflora

Puyvelde et al. (1989) stated that the H_2O extract of *H. triflora* leaves prohibited the barbiturate sleeping time prolongation associated with carbon tetra chloride (CCl_4)-induced liver damage in mice at dose 200 mg/kg, compared to pentobarbital (40 mg/kg). This effect was due to benzoic acid. The isolated benzoic acid produced a significant reduction of the high levels of glutamate pyruvate transaminase (GPT) and glutamyl oxalacetate transaminases (GOT) induced by CCl_4 administration (Puyvelde et al., 1989).

Hypoestes verticillaris

Two phenanthroindolizidine alkaloids: hypoestestatins 1 (**34**) and 2 (**35**) have been separated from the East African *H. verticillaris* shrub. They possessed marked growth inhibitory potential towards murine lymphocytic leukemia (P-388) (ED_{50} 10^{-5} µg/mL) (Pettit et al., 1984).

Hypoestes aristata

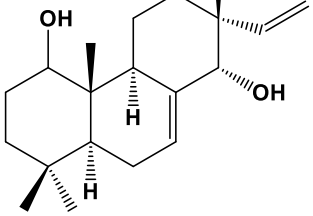
In resazurin fluorescent assay, the leaves extract of *H. aristata* displayed cytotoxic potential towards human drug sensitive T-lymphoblastoid (CCRF-CEM) and multidrug-resistant T-lymphoblastoid (CEM/ADR5000) leukemia cells with IC_{50}s 2.28 and 3.8 µg/mL, respectively (Saeed et al., 2016).

Hypoestes purpurea

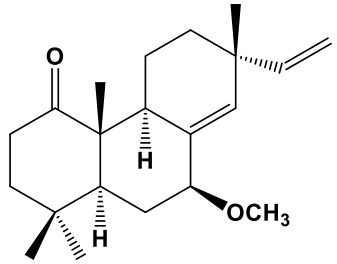
The separation and purification of the constituents obtained from the extract of *H. purpurea* aerial parts afforded furanolabdane diterpenes: hypopurins A-D (**8**-**11**), lignans: α-O-methylcubebin (**36**), helioxanthin (**38**), hinoquinin (**37**), 7-hydroxyhinokinin (**41**), justicidine E (**39**), dehydroxycubebin (**40**), and (-)-hibalactone (**42**), and triterpenes: betulin (**45**) and lupeol (**44**) (Shen et al., 2004). Hypopurins A-D (**8**-**11**) were assessed for cyctotoxicity *in vitro* in 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay towards the epidermoid carcinoma (KB) cell line. Hypopurin A (**8**) had moderate cytotoxic potential with an IC_{50} 9.4 µM, whereas, the other metabolites were inactive (IC_{50} > 100 µM) (Shen et al., 2004).

Hypoestes serpens

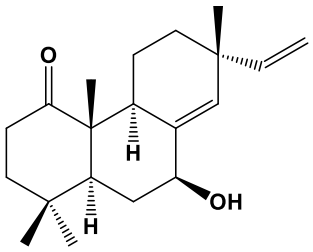
The isopimarane diterpenes: 14α-hydroxyisopimara-7,15-dien-1-one (**28**), 7β-hydroxyisopimara-8,15-dien-14-one (**27**), 1β,14α-dihydroxyisopimara-7,15-diene (**29**), 7β-acetoxyisopimara-8(14),15-dien-1-one) (**30**), and 7β-hydroxyisopimara-8(14),15-dien-1-one (**31**) were separated from *H. serpens* leaves. These metabolites were assessed for their antifungal potential towards *Cladosporium cucumerinum* and *Candida albicans* and acetylcholinesterase inhibitory activities (Rasoamiaranjanahary et al., 2003a). All compounds displayed antifungal activity against both plant pathogenic fungi: *C. cucumerinum* and *C. albicans*.



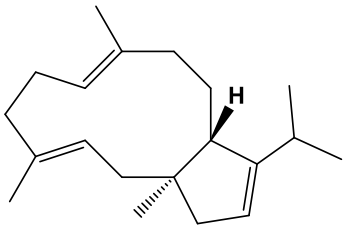
1β,14α-Dihydroxyisopimara-7,15-diene (29)



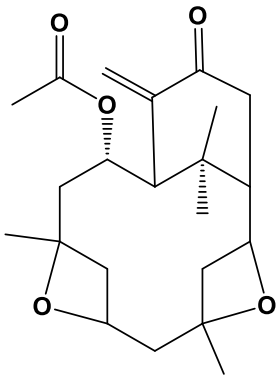
7β-Acetoxyisopimara-8(14),15-dien-1-one (30)



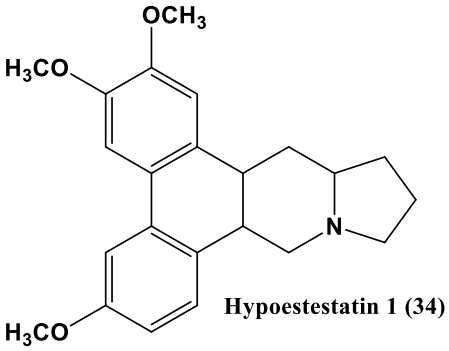
7β-Hydroxyisopimara-8(14),15-dien-1-one (31)



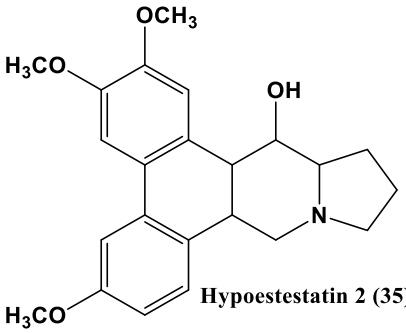
Dolabeserpenoic acid A (32)
(3*E*,7*Z*)-Dollabella-3,7,12-trien-17-oic acid



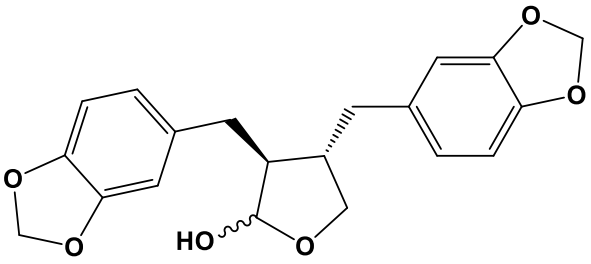
Hypoestoxide (33)



Hypoestestatin 1 (34)

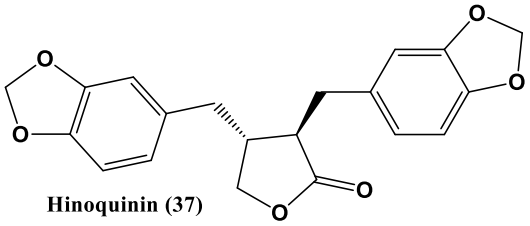


Hypoestestatin 2 (35)

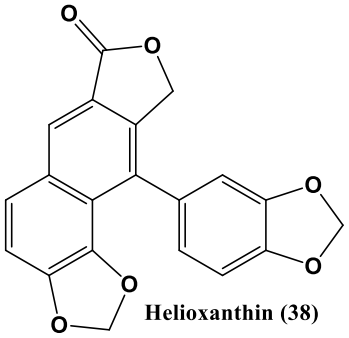


α-O-Methylcubebin (36)

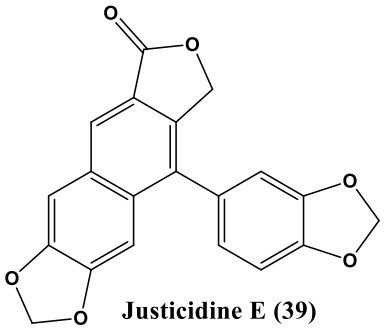
Figure 5: Chemical structures of compounds **29-36**



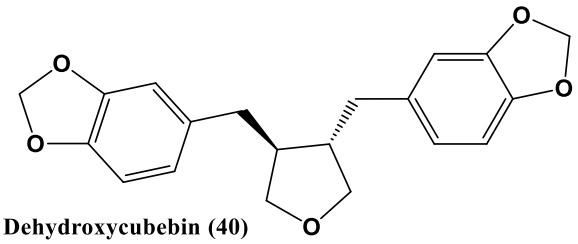
Hinoquinin (37)



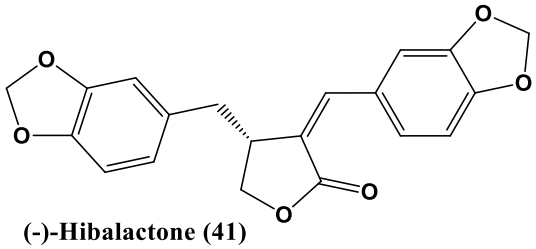
Helioxanthin (38)



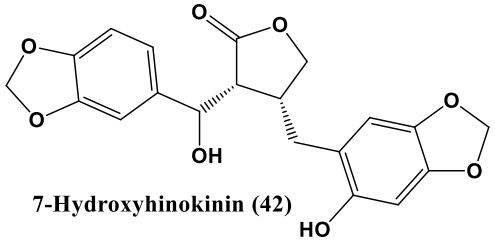
Justicidine E (39)



Dehydroxycubebin (40)



(-)-Hibalactone (41)



7-Hydroxyhinokinin (42)

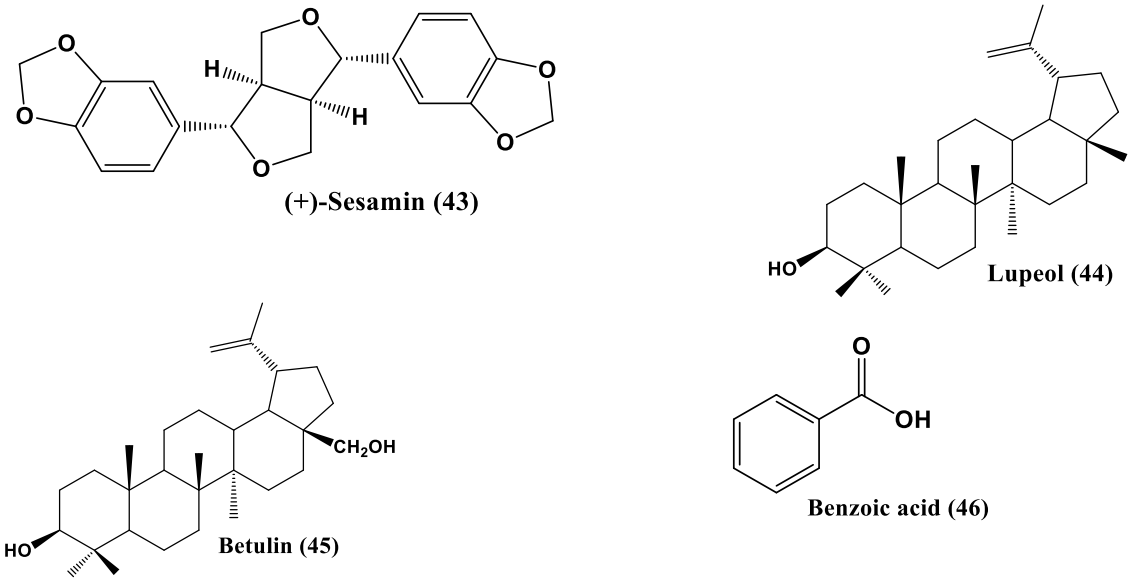


Figure 6: Chemical structures of compounds **37-46**

Compounds **28** and **30** were the most potent compounds minimum inhibitory concentration (MIC) 0.5 µg) in the thin layer chromatography (TLC) bioautographic assay, compared to miconazole (MIC 1 µg). 7β-Hydroxyisopimara-8,15-dien-14-one (**27**) had the same MIC value as miconazole. The other compounds **29** and **30** were slightly active with MICs 25-50 µg towards *C. albicans* and *C. cucumerinum*. As *C. albicans* is one of the causative agents of vaginitis. The inhibitory potential of these compounds towards *C. albicans* supported the use of *H. serpens* in traditional medicine to treat vaginitis. Moreover, **27** and **28** also exhibited acetylcholinesterase inhibitory potential. The MICs in a TLC bioautographic assay were determined as 0.5 µg for 7β-hydroxyisopimara-8,15-dien-14-one (**27)** and 0.2 µg for 14α-hydroxyisopimara-7,15-dien-1-one (**28**) (Rasoamiaranjanahary et al., 2003a), compared to galanthamine alkaloid (0.01 µg), which was introduced recently for treating Alzheimer's disease. Rasoamiaranjanahary et al. (2003b) reported the separation of dolabeserpenoic acid A (**32**) and fusicoserpenol A (**26**) with antifungal potential from *H. serpens* leaves. The MICs were 5 and 2 µg, respectively for **26** and 5 µg for **32** towards both *C. cucumerunum* and *C. albicans* in the TLC bioautographic assay, compared to miconazole (MIC 1 µg) (Rasoamiaranjanahary et al., 2003b).

H. serpens alcohol extract afforded serpendione (**16**). The alcohol extract at concentrations 0.5, 1, and 1.5 mg/mL had a good relaxant activity (ED_{50} 1.19 mg/mL) against contraction induced by noradrenaline with 7.50, 19.55, and >100% reduction, respectively. Serpendione (concentration (Conc.) 0.05 mg/mL) strongly repressed the maximal responses to the contractile agent with 92.2% inhibition. These results validate the utilization of *H. serpens* as a herbal medicine for treating hypertension (Andriamihaja et al., 2001).

Hypoestes rosea

Adesomoju et al. (1983a) purified hypoestoxide (HE, **33**) from *H. rosea* leaves and twigs extracts (Adesomoju et al., 1983a). It frustrated IL-6, IL-1β, and TNF-α production in lipopolysaccharide (LPS)-activated normal human peripheral blood mononuclear cells. Moreover, HE prohibited the nitric oxide (NO) production by interleukin-1β (IL-1β) or IL-17-stimulated normal human chondrocytes. HE oral administration to mice significantly ameliorated hind paw edema induced by antibodies to type II collagen plus LPS. Furthermore, its topical administration to mice also produced remarkable inhibition of ear inflammation induced by phorbol ester. The anti-inflammatory potential of HE may be due to its capacity to prohibit NF-kB activation through direct kappa-B kinase subunit alpha (IKK) inhibition. Thus, HE could have a significant effect in treating different inflammatory disorders and may represent a novel class of IKK inhibitors (Ojo-Amaize et al., 2001; Adesomoju 1983a).

It has been reported that HE inhibited mouse melanoma (B16F1) in the tumor model C57BL/6 mice. Ojo-Amaize et al. (2007a) demonstrated that mean tumors volumes in mice treated with HE orally alone or combined with 5-fluorouracil (5-FU) were significantly smaller (> 60%) than those in control mice (471.2 mm^3 *vs* 1542.8 mm^3) in the in ovo chick chorioallantoic membrane (CAM) assay. The remarkable reductions in tumor led to increase in life spans (ILS) and prominent survival times mean (STM) in the treated mice. These results indicated that HE is an efficient anticancer agent for colorectal cancer (CT26.WT) alone or in combination with 5-FU (Ojo-Amaize et al., 2007a). The tumor inhibitory action of HE is due to its capability to arrest cell cycle at G_2-M phase by the interfering with actin assembly, inhibiting angiogenesis, migration of the endothelial cell, and vascular endothelial growth factor (VEGF)-induced cell proliferation (Flis et al., 2006). In contrast, 5-FU triggered apoptosis by depleting thymidine through direct incorporation into deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and thymidine synthase inhibition (Wada et al., 2006). Low doses combination of 5-FU and HE enhanced the 5-FU anti-tumor responses Ojo-Amaize et al.,

2001; 2002). Interestingly, the consumption of the dried leaf powder of *H. rosea* as a supplement led to the removal of the existing intestinal polyps in human (Ojo-Amaize et al., 2007a). Also, HE inhibited the *in vitro* growth of various murine and human tumor cell lines at concentrations 0.3 to 10 µM. Also, it was inactive in the Ames test as a mutagen. HE possessed a strong potency (Conc. 0.3-10 mg/kg) towards P-388D1 leukemia in C57BL/6 × DBA/2 F_1 and mouse melanoma (B16) cell growth in C57BL/6 mice. At a low maximal effective dose of 5 mg/kg, HE had a promising *in vivo* antitumor potential that was comparable with or better than cortisone acetate, bleomycin, vincristine, 5-fluorouracil, adriamycin, etoposide, and cyclophosphamide. HE prohibited the HeLa (cervical epitheloid carcinoma) and human Burkitt lymphoma (CA46) cells growth in the cell cycle G2-M phase, which caused either indirect or direct interference with actin assembly. Thus, the arrest in the cell cycle took place at cytokinesis as observed by the increase in binucleate cells number. Moreover, HE prohibited *in vitro* vascular endothelial growth factor-induced cell proliferation with an IC_{50} 28.6 µM and significantly inhibited basic fibroblast growth factor-induced angiogenesis on the chick chorioallantoic membrane with an IC_{50}10 µM. Furthermore, HE inhibited migration of endothelial cells on collagen, vitronectin, and fibronectin (Ojo-Amaize et al., 2002). Ojo-Amaize et al., (2007b) stated that HE had a relatively weak *in vitro* activity with IC_{50} 10 µM, compared to chloroquine IC_{50} 0.11 µM towards various strains of *P. falciparum*. The suppressive dose (SD_{90}) of HE (SD_{90} 250 µg/kg) is much lower than chloroquine (SD_{90} 5 mg/kg) (Ojo-Amaize et al., 2007b). It was speculated that the α,β-unsaturated ketone substructure of HE may interfere with the parasite mitochondrial electron transport as in β-methoxyacrylates (Ojo-Amaize et al., 2007b; Alzeer et al., 2000). HE inhibited the sporozoites motility and endothelial cell migration, also interfered with cytokinesis and actin assembly (Ojo-Amaize et al., 2007b; Tardieux et al., 1998).

Conclusion

This works provides a background for the future studies on *Hypoestes* species, particularly the species, which have not been extensively explored for separation and characterization of bioactive constituents and pharmacological potentials. Further investigations of these species are guaranteed to identify the bioactive metabolites responsible for diverse pharmacological and biological effects.

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