Phytochemistry and pharmacology of the genus *Drypetes*: A review

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ABSTRACT

Aims: Traditional medicinal use of species of the genus *Drypetes* is widespread in the tropical regions. The aim of this review is to systematically appraise the literature available to date on phytochemistry, ethnopharmacology, toxicology and bioactivity (*in vitro* and *in vivo*) of crude extracts and purified compounds.

Ethnopharmacological relevance: Plants of the genus *Drypetes* (Putranjivaceae) are used in the Subsaharan African and Asian traditional medicines to treat a multitude of disorders, like dysentery, gonorrhoea, malaria, rheumatism, sinusitis, tumours, as well as for the treatment of wounds, headache, urethral problems, fever in young children, typhoid and several other ailments. Some *Drypetes* species are used to protect food against pests, as an aphrodisiac, a stimulant/depressant, a rodenticide and a fish poison, against insect bites, to induce conception and for general healing. This review deals with updated information on the ethnobotany, phytochemistry, and biological activities of ethnomedicinally important *Drypetes* species, in order to provide an input for the future research opportunities.

Methods: An extensive review of the literature available in various recognized databases *e.g.,* Google Scholar, PubMed, Science Direct, SciFinder, Web of Science, www.theplantlist.org and www.gbif.org, as well as the Herbier National du Cameroun (Yaoundé) and Botanic Gardens of Limbe databases on the uses and bioactivity of various species of the *Drypetes* was undertaken.

Results: The literature provided information on ethnopharmacological uses of the Subsaharan African and Asian species of the genus *Drypetes*, *e.g., Drypetes aubrévillii, D. capillipes, D. chevalieri, D. gerrardii, D. gossweileri, D. ivorensis, D. klainei, D. natalensis, D. pellegrini* (all endemic to Africa) and *D. roxburghii* (Asian species), for the treatment of multiple disorders. From a total of 19 species, more than 140 compounds including diterpenes, sesquiterpenes, triterpenes (friedelane, oleanane, lupane and hopane-type), flavonoids, lignans, phenylpropanoids and steroids, as well as some thiocyanates, were isolated. Several crude extracts of these plants, and isolated compounds displayed significant analgesic, anthelmintic, antidiabetic, anti-emetic anti-inflammatory, antioxidant, antiparasitic, central nervous system depressant, cytotoxic, and insecticidal activities both *in vitro* and *in vivo*. Some toxicities associated with the stem, bark, seed and leaf extracts of *D. roxburghii*, and the flavonoid, amentoflavone, isolated from the stem extract of *D. littoralis* as well as *D. gerrardii*, were confirmed in the animal models and in the rat skeletal myoblast cells assays. As a consequence, traditional medicine from this genus should in future be applied with care.

Conclusions: Plants of this genus have offered bioactive samples, both from crude extracts and pure compounds, partly validating their effectivity in traditional medicine. However, most of the available scientific litteratures lacks information on relevant doses, duration of the treatment, storage conditions and positive controls for examining bioefficacy of extract and its active compounds. Additional

toxicological studies on the species used in local pharmacopeia are urgently needed to guarantee safe application due to higth toxicity of some crude extracts. Interestingly, this review also reports 10 pimarane dinorditerpenoids structures with the aromatic ring C, isolated from the species collected in Asia *Drypetes littoralis* (Taiwan), *D. perreticulata* (China), and in Africa *D. gerrardii* (Kenya), *D. gossweileri* (Cameroon). These compounds might turn out to be good candidates for chemotaxonomic markers of the genus.

Keywords: *Drypetes*, Ethnopharmacology, Chemical constituents, Bioactivities

1. Introduction

The genus *Drypetes*, previously put in Euphorbiaceae family, has been included within the Putranjivaceae based partly on the presence of the mustard oils in their leaf tissus, a compound they share with the genus *Putranjiva* in this family and because its was the sole pantropical zoochorous genus of the Euphorbiaceae. The Putranjivaceae was formerly a tribe (Drypeteae) of the subfamily Phyllanthoideae in the Euphorbiaceae. When the Phyllanthoideae was separated to form the new family Phyllanthoideae, it was decided that Drypeteae also could stand alone (APG III, 2009). The greatest diversity of the genus *Drypetes* is found in Asia, with about 120 known/documented species. Approximately 75 species grow in Africa and Madagascar, with around 20 species, many of them as yet unexplored, found in the Americas. Most species are narrowly distributed, but *D. roxburghii* is found in seasonal forests from Pakistan to Indonesia (Levin, 2014). Plants of the genus *Drypetes* are trees or shrubs, with alternate, coriaceous or chartaceous and entire or toothed leaves; stipules are caducous and rarely persistent. Pedicellate male and female flowers are arranged in bundles in the axils of the leaves, or are produced on older branches or the stem. Flowers of this genus are dioecious and petals absent: male flowers have globose buds, and four or five broad, imbricate, usually coraceous septals. Typically, three or more stamens are inserted around and at the base of a central flat concave or occasionally cupular disk, and filaments are free. Anthers are erect and often large with parallel cells dehiscing longitudinally, and a rudimentary ovary is either absent or represented by a small conical protrusion in the middle of the disk. In common with the male flower the female version display a calyx, with a hypnogynous annular or cupular disk. The ovary has between one and four cells with 2 ovules in each cell; styles are short or absent and stigmas thick, flattened, bifid or undivided and more or less reniform. Fruits are globose, ellipsoid or ovoid and indehiscent with a thick, woody pericarp surrounding a solitary seed (by abortion) with fleshy albumen displays 1-4 cells. The embryo is straight with flat, broad cotyledons (Baker, 1913).

The classification developed by Pax and Hoffmann in 1922, although still valid today, is not completely congruent with postulated phylogenetic (Fig. 1) and evolutionary relationships (Wurdack

et al., 2004, Levin, 2014). For example, *Drypetes roxburghii* (Wall.) Hurus. (Synonym: *Putranjiva roxburghii* Wall.) is the accepted name. Thus, this review aims to present a synopsis on the ethnopharmacological uses and more than 140 secondary metabolites produced by the members of the *Drypetes* genus. In addition, bioactivities of assayed extracts and chemical constituents are also presented.

Figure 1: *Drypetes* and *Putranjiva* clades within the subfamily Phyllanthoideae (shaded tree), family Euphorbiaceae (shaded column), "group" Putranjivaceae: Molecular phylogenetic analysis using plastid rbcL DNA sequences (Wurdack *et al.*, 2004).

2. Materials and methods

In order to assess the uses, chemical constituents and bioactivities of the crude extract as well as isolated compounds from the genus *Drypetes*, a wide range of literature sources were interogated (*e.g.* Google Scholar, PubMed, Science Direct, SciFinder, Web of Science, as well as the Herbier National du Cameroun (Yaoundé) and Botanic Gardens of Limbe databases). Critical reviews of plant taxonomy were sourced from www.theplantlist.org and plant occurrence from www.gbif.org. Relevant bibliographic items were identified systematically in the relevant libraries by searching for key terms including *Drypetes*, ethnobotany, ethnopharmacology, medicinal plants, chemical constituents, etc. Initially other terms were considered such as natural products, pharmacognosy, folk medicine and botany, but then excluded since their use did not result in relevant references. Four libraries with holdings both on useful/medicinal plants/pharmacognosy and the history of medicine/pharmacy were selected: Le Museum National d'Histoire Naturelle de Paris, The School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Herbier National du Cameroun, Yaoundé and Botanic Gardens of Limbe, Cameroon. These libraries contain relevant literature, which span a wide time period and most importantly cover the period prior to the introduction of electronic databases. The books chosen were searched for relevant information. Most but not all sources are written in English.

3. Results and discussion

3.1. Traditional medicinal use of species of the *Drypetes* genus

Various species of the genus *Drypetes* are narrowly distruibuted in tropical forested areas of Asia and utilised in a range of mostly unreported traditional medicinal applications. *D. roxburghii*, however, has wide ranging traditional medicinal applications for its fruits, seeds and leaves from Pakistan to Indonesia. This species is also found in the tropical Americas, and was introduced to Subsaharan Africa decades ago for medicinal purposes. In Subsaharan Africa, nine *Drypetes* species are used in traditional medicines, with the bark having multiple, prominent medical uses. Ethnopharmcological information on the *Drypetes* genus goes back to data collected from African species by Ainslie (1937), Bouquet (1969), Bouquet and Debray (1974), Burkill (1985), Cooper and Record (1931), Dalziel and Hutchinson (1937), Kerharo and Bouquet (1950), and Rapoda-Walker and Sillans (1961). Further ethnomedicinal knowledge on African and Asian species has been added by natural products chemists in the course of chemical and pharmacological investigations (table 1).

Table 1. Ethnomedicinal uses of the species of the *Drypetes* genus

Name of species	Country/Province	Ethnomedicinal uses	Type of recipe	References
***D. aubrévillei* Leandri**	Guinea, Liberia, Ghana and Ivory Coast	Healing on the skin and mucosa	Bark and fruit	Burkill (1985)
		Pulmonary disorders and analgesic	Bark	
		Antipyretic	Unspecified parts	
	Liberia	Fever, rheumatism and general fatigue	Decoction of macerated bark and fruit	Cooper and Record (1931)
	Elsewhere	Blotchy skin, locally as "dishcloth"	Powdered stem bark	
		Expectorant and bronchial decongestant	Pap made from the bark	Bouquet and Debray (1974)
***Drypetes capillipes* (Pax) Pax & K. Hoffm.**	Central African countries	General analgesia	Leaves and bark	Burkill (1985)
	Congo (Brazzaville)	Mouth-wash for severe toothache, and an enema for kidney-pains	Bark decoction	Bouquet (1969)
		Topical massage for stiffness of the neck	Leaves	
***Drypetes chevalieri* Beille ex Hutch. & Dalziel**	Cameroon	Tumours, swellings, inflammation and gonorrhoea	Whole plant	Dalziel and Hutchinson, (1937); Bouquet and Debray (1974)
	'Kru' and the Guere of Liberia	Dysentery	Sap expressed from leaves and twigs	Kerharo and Bouquet (1950)
	Ivory Coast	head-colds and sinusitis	Powdered leaves	
	West tropical Africa	Intestines; pulmonary troubles and naso-pharyngeal affections	Leaves	Burkill (1985)
		Diarrhoea and dysentery	Sap expressed from leaves and twigs	
***Drypetes gerrardii* Hutch**	Coast province, Kenya	Malaria and other ailments	Unspecified parts	Ng′ang′ a et al. (2011)
***Drypetes gossweileri* S. Moore; synonym: *D. armoracia* Pax & K. Hoffm.**	Democratic Republic of Congo, Gabon, Equatorial Guinea, Central African Republic and Cameroon	General healing	Roots	Burkill (1985)
		Analgesia, vermifuge, genital stimulant/depressant, against veneral diseases, as febrifuge, reptile-repellent, and as fish-poison	Bark	
	Western Cameroon	gonorrhoea and toothache	Bark	Dalziel and Hutchinson, (1937)
	Central African Republic	Helminthic diseases, rheumatism, fever and malaria	Unspecified parts	Ngoupayou et al. (2003); Tchinda and Sob, (2008); Raponda-Walker and Sillans (1961)
		Poison fishing	Bark and fruit	Raponda-Walker and Sillans (1961)
	Gabon	Anthelminthic	Bark-macerate or decoction with pepper	Bouquet (1969); Akendengue and Louis (1994)
		Rheumatism, headaches, general pain, body-pains, helminths and filariasis	Bark	
		Wounds and for toothache	Roots	Troupin (1982)
		Poison fishing	Bark and fruit	Raponda-Walker and Sillans (1961)
	Congo (Brazzaville)	Vermifugal enema	Bark-macerate or decoction with pepper	Bouquet (1969)
		Urethral discharge or as an aphrodisiac	Bark powder is cooked together with bananas	
		Fever in young children	Powder-decoction is added to bath water	
		Repel snakes	Boiled bark water	
		Antipyretic, analgesic, aphrodisiac, for body pain, headache and urethral problems	Bark	

	Nkundo region of Congo	Back pain, insect bites, and dental caries	Bark shavings rubbed onto skin	
		Otitis	Stem bark juice	Muganza et al. (2012)
	Nigeria	Deep wounds	Roots are powdered with kola and *Celtis integrifolia*	Ainslie (1937)
	Central African Republic	Protect food against pests	Bark	Aba et al. (2013); Motte, (1980)
		Fever, malaria and typhoid	Bark	Kajode et al. (2008).
***Drypetes ivorensis* Hutch. & Dalziel**	Liberia, Cameroon, Ghana, Ivory Coast, and Gabon	Skin and mucosa treatments; rodenticide, mammal and bird poison	Bark and fruit	Burkill (1985)
	Ivory Coast	Dressings to mature boils and carbuncles. Poison bait for rats, mice and other noxious animals	Bark	Kerharo and Bouquet (1950); Bouquet and Debray (1974)
***Drypetes klainei* Pierre ex Pax**	Central African Republic	Analgesic, vermifuge and fish poison	fruit	Raponda-Walker and Sillans (1961); Burkill (1985)
	Gabon	Rheumatism, and anthelminthic	Macerate or decoction of fresh bark	Raponda-Walker and Sillans (1961);
***Drypetes natalensis* (Harv.) Hutch**	Tanzania	Malaria and other ailments	Unspecified parts	Gessler et al. (1995)
***Drypetes pellegrini* Leandri**	Ivory Coast	Ivorian multi-purpose medicine	Bark	Aubréville (1959)
***Drypetes roxburghii* (Wall) Hurus**	India	Catarrh, skin disease, fever, cold, rheumatism, inflammation, sterility, as aphrodisiac, a tonic to aid conception, muscle twisting, arthralgia and for of filarial diseases	Leaves, fruit and seeds	Chopra et al. (1970b); Kumar (2014c); Shahwar et al. (2012); Sudharshan et al. (2009); Thakur 2011
		Insect bites	Crushed seeds	Kumar et al. (1998)
		spread on the maternity room floor for an easy delivery	Scattered leaves	
		worn to protect from red pimples and allergy	Garland of its dried seeds	Singh and Bisht (1999)
		Dysentery, fever, viral fever, spermopoietic, optic lavage to wash infected eyes, laxative, elephantiasis and sterility	Leaf sap	Singh et al. (2010); Kumar and Chaturvedi 2010; Singh and Dubey (2012)
		Cold, fever, rheumatism and swollen throat	Decoction of leaves and the bark	Pandey and Tripati (2011); Maurya and Dongarwar 2012; Sharma and Bhadange (2013); Sreeramulu et al. (2013)
		Pain and aid conception	A paste composed of the seeds; A leaf poultice along with the leaves of *Dalbergia sissoo* and *Vitex negundo*	Kumar (2012).
	Bangladesh	Curative properties and cardiovascular diseases	Unspecified parts	Mollik et al. 2(009).
		Gastrointestinal disorders	250 mg of powdered seeds are taken every 4 h with a little sugar and water	Kadir et al. (2013)

An overview on, the occurrence and traditional use of this plants is presented below.

3.1.1. *Drypetes aubrévillei* Leandri

Drypetes aubrévillei Leandri (locally called “Duamoko” in West African countries) grows in the West African countries of Guinea, Liberia, Ghana and Ivory Coast. The bark and fruit are used for general healing on the skin and mucosa, while the bark alone is utilised for pulmonary disorders and analgesic applications. Unspecified parts of the plant are also used as a febrifuge (antipyretic) (Burkill, 1985). In Liberia, a decoction of macerated bark and fruit is used as a liniment for application in fever,

rheumatism and general fatigue; elsewhere, powdered stem bark is applied to treat a blotchy skin condition referred to locally as “dishcloth” (Cooper and Record, 1931). Pap made from the bark is also used as an expectorant and bronchial decongestant (Bouquet and Debray, 1974).

3.1.2. *Drypetes capillipes* (Pax) Pax & K. Hoffm.

Drypetes capillipes (Pax) Pax & K. Hoffm. (locally called “mò.kàmá” in Central African countries, and “gbólóga” by Baka Pygmies) grows in the Central African countries, Democratic Republic of Congo, Cameroon, Gabon, Equatorial Guinea and Central African Republic. The leaves and bark are widely used for general analgesia (Burkill, 1985). In Congo (Brazzaville), a bark decoction is used as a mouth-wash for severe toothache, and an enema for kidney-pains, while the leaves are applied in topical massage for stiffness of the neck (Bouquet, 1969).

3.1.3. *Drypetes chevalieri* Beille ex Hutch. & Dalziel

Drypetes chevalieri Beille ex Hutch. & Dalziel (locally called in Nigeria, “sunsun-iro” or “aya” by Yoruba and “owe” or “aghedan” by Edo) is found in Ivory Coast, Liberia, Gabon, Cameroon, Central African Republic, Ghana, Equatorial Guinea and The Democratic Republic of Congo. In Cameroon, the plant is used locally for the treatment of tumours, swellings, inflammation and gonorrhoea (Dalziel and Hutchinson, 1937; Bouquet and Debray, 1974). Sap expressed from leaves and twigs is taken in draught by the ‘Kru’ and the Guere of Liberia for dysentery, and the powdered leaves are sometimes used in Ivory Coast as a snuff for head-colds and sinusitis (Kerharo and Bouquet, 1950). The leaf is used in west tropical Africa for "intestines"; pulmonary troubles and naso-pharyngeal affections, while the sap is used against diarrhoea and dysentery (Burkill, 1985).

3.1.4. *Drypetes gerrardii* Hutch; synonym: *Drypetes gerrardii var. gerrardii*

Drypetes gerrardii Hutch (locally called “Itulelei tree” in Kenya) grows in Kenya, United Republic of Tanzania, Malawi, South Africa, Mozambique, Uganda and Swaziland, and is reported to be used to treat malaria and other ailments among 'Chonyi' people in Kilifi District, Coast province, Kenya (Ng′ang′ a *et al.*, 2011).

3.1.5. *Drypetes gossweileri* S. Moore; synonym: *D. armoracia* Pax & K. Hoffm.

Drypetes gossweileri S. Moore (locally called “horseradish tree” in English; “bologa” or “kode” or “olelang” in Cameroon; “gama”or “n´zongo” or “ngama” in Central African Republic; “bonsole”, “boshimi” or “muyuyungu” or “pilipili” or “vungu” or “yungu” in Congo; “akot” or “ossôgho” in Gabon; “agawo” or “okhuaba” in Nigeria) is found in the Democratic Republic of Congo, Gabon, Equatorial Guinea, Central African Republic and Cameroon. While the root is applied for general healing, the bark is used for analgesia, vermifuge, genital stimulant/depressant, against veneral diseases, as febrifuge, reptile-repellent, and as fish-poison (Burkill, 1985). In Western Cameroon, the bark is adminstered for the treatment of gonorrhoea and toothache (Dalziel and Hutchinson, 1937), while unspecified parts of the plant are also used in the Central African Republic against helminthic

diseases, rheumatism, fever and malaria (Ngoupayou, 2003, Tchinda and Sob, 2008, Raponda-Walker and Sillans, 1961). Bark and fruit are used for poison fishing (Raponda-Walker and Sillans, 1961). Furthermore, a bark-macerate or decoction with pepper is used in Gabon as an anthelminthic, and in Congo (Brazzaville) as a vermifugal enema (Bouquet, 1969). In addition, the bark is used in the treatment of rheumatism, headaches, general pain, body-pains, helminths and filariasis in Gabon (Raponda-Walker and Sillans, 1961; Bouquet, 1969; Akendengue and Louis, 1994), whereas the roots are applied to wounds and for toothache (Troupin, 1982). In Congo, the bark powder is cooked together with bananas and taken to relieve urethral discharge or as an aphrodisiac, while a powder-decoction is added to bath water for the relief od fever in young children. The bark is also reported to repel snakes, if a piece is kept in the hut-roof, or boiled bark water is sprinkled around the perimeter of the hut (Bouquet, 1969). In the Nkundo region of Congo bark shavings are rubbed onto skin for the treatment of rib or back pain, insect bites, and is also placed under the affected tooth in the case of dental caries. Stem bark juice is administered otically against otitis (Muganza *et al.,* 2012), and certain populations in Congo use bark preparations as an antipyretic, analgesic and aphrodisiac, for body pain, headache and urethral problems, respectively (Bouquet, 1969). Bark and fruit are used as fish-poison in Gabon (Raponda-Walker and Sillans, 1961), and in Nigeria, the roots are powdered with kola and *Celtis integrifolia* to treat deep wounds (Ainslie, 1937). Like in Gabon, the bark is used by the Aka pygmies and the Monzombo people in the Central African Republic for poison fishing, and the plant is also used in the Boukoko area during postharvest to protect food against pests (Aba *et al.,* 2013, Motte, 1980). Finally, medicines from the bark are prepared by local people in Osun State for the treatment of fever, malaria and typhoid (Kajode *et al.,* 2008).

3.1.6. *Drypetes ivorensis* Hutch. & Dalziel; synonym: *Drypetes pierreana* A. Chev.

Drypetes ivorensis Hutch. & Dalziel (locally called “Kpahn-wee”) grows in Liberia, Cameroon, Ghana, Ivory Coast, and Gabon. The bark and fruit are used in skin and mucosa treatments, while the bark is additionally applied as a rodenticide, mammal and bird poison (Burkill, 1985). Furthermore, bark and fruit are used to prepare dressings to mature boils and carbuncles. The bark is considered toxic in Ivory Coast, and is used by the Akye to prepare poison bait for rats, mice and other noxious animals (Kerharo and Bouquet, 1950; Bouquet and Debray, 1974).

3.1.7. *Drypetes klainei* Pierre ex Pax

Drypetes klainei Pierre ex Pax (locally called “zogre or rokobasoki or rokobasole”) grows in Liberia, Cameroon, The Democratic Republic of Congo, Central African Republic, and Gabon. The bark of this plant is widely used as an analgesic and vermifuge, and together with the fruit as a fish poison (Raponda-Walker and Sillans, 1961; Burkill, 1985). In Gabon, a macerate or decoction of fresh bark is applied topically for treatment of rheumatism, and with a piment internally as an anthelminthic (Raponda-Walker and Sillans, 1961).

3.1.8. *Drypetes natalensis* (Harv.) Hutch; synonym: *Drypetes natalensis* var. *natalensis*

Drypetes natalensis (Harv.) Hutch (locally called “Natal drypetes or Natal ironplum” in English; *in* Southern Africa: “Natalsysterpruim, stinkbos, iKushwane elikhulu, umBejiza, umGunguluza, umGunguluzane, umKushwane” by Zulu and “umKhiwane” by Xhosa) grows in Mozambique, Tanzania, South Africa, Kenya, and Malawi. It is predominantly used for the treatment of malaria and other ailments in Tanzania (Gessler *et al.*, 1995).

3.1.9. *Drypetes pellegrini* Leandri; synonym: *Drypetes vignei* Hoyle

Drypetes pellegrini Leandri (locally called “omenewa-hoakoa” in Ghana) is endemic to Ghana and Ivory Coast. The bark is used as an Ivorian multi -purpose medicine (Aubréville, 1959).

3.1.10. *Drypetes roxburghii* (Wall.) Hurus.; synonym: *Putranjiva roxburghii* Wall.

Drypetes roxburghii (Wall.) Hurus. (locally called “Amulet-Plant or Wild Olive or Child-Life-Tree” in India) grows in The United States, India, Papua New Guinea, Taiwan, and Trinidad and Tobago; it was introduced for cultivation to Subsaharan countries for a variety of medicinal applications. The leaves are used in India in the treatment of catarrh, skin disease, fever, cold, rheumatism and sterility (Chopra *et al.*, 1970b), and fruit, seeds and leaves have various application as an aphrodisiac, a tonic to aid conception and for the treatment of filarial diseases (Kumar, 2014c). Crushed seeds are applied to insect bites by the S-Pitonj, MP-Pitinjia, and M-Pitaunji tribes in the Bihar region, India (Kumar *et al.*, 1998); the leaves and fruit are also used in India for the treatment of muscle twisting, arthralgia and rheumatism (Shahwar *et al.*, 2012). Among the tribes of Uttar Pradesh, India, scattered leaves are spread on the maternity room floor for an easy delivery, and a garland of its dried seeds is worn to protect from red pimples and allergy (Singh and Bisht, 1999). Unspecified parts of the tree are reported to be used in India against cold, fever, rheumatism and inflammation (Sudharshan *et al.*, 2009). In the 'Chatara' block of district Sonebhadra, Uttar Pradesh, India against various parts of the plant are used to treat cold, dysentery, fever, as well as an aphrodisiac, stimulant and spermopoietic; leaf sap is used as an optic lavage to wash infected eyes (Singh *et al.*, 2010). In the Vidarbha region, Maharashtra, India, the leaf is used for the treatment of viral fever (Kumar and Chaturvedi, 2010). In Gorakhpur division, India, leaves and stones are given as a decoction for cold, fever and rheumatism (Pandey and Tripati, 2011), and tribes of the Sirmour district, Himanchal Pradesh, India, orally apply the nuts to aid conception and promote the birth of a male child (Thakur, 2011). In Nagpur, India, the plant is traditionally applied used for coughs, cold and fever (Maurya and Dongarwar, 2012). The fruit is used in the District of Uttar Pradesh, India as an aphrodisiac, antiinflammatory, for habitual abortion, as a laxative in addition to the treatment of elephantiasis, eye infection and sterility (Singh and Dubey, 2012). A paste composed of the seeds is given traditionally applied to the forehead for the treatment of pain; seeds are also taken orally, for around one month, by women trying to conceive.

A leaf poultice along with the leaves of *Dalbergia sissoo* and *Vitex negundo* is applied for the treatment of joint pain (Kumar, 2012). Traditional use of the leaves and fruit against cold, rheumatism, and swollen throat in India has also been reported (Sharma and Bhadange, 2013). The bark is applied by the local people in Nalgonda and Warangal districts of Andhra Pradesh, India for the treatment of cough (Sreeramulu *et al.*, 2013). In the Khulna division, Bangladesh it is used for its curative properties in folk medicine for the treatment of cardiovascular diseases (Mollik *et al.*, 2009). Traditional healers in Bangladesh apply the plant for the treatment of gastrointestinal disorders: 250 mg of powdered seeds are taken every 4 h with a little sugar and water (Kadir *et al.*, 2013).

3.2. Phytochemistry

Chemical investigation of the species of the *Drypetes* genus began when Puntambekar (1950) reported three thiocyanate-derived compounds, 1-thio-*β*-D-glucopyranose-2-methyl-*N*-(sulfooxy)propanimidoyl (glucoputranjivin, **1**), (2*S*) 1-thio-*β*-D-glucopyranose-*N*-(sulfooxy)-*sec*-butylanimidoyl (glucojiaputin, **2**) and its isomer (2*R*) 1-thio-*β*-D-glucopyranose-*N*-(sulfooxy)-*sec*-butylanimidoyl (glucococchlearin, **3**) from the steam volatile oil of wet kernels of the Asian *D. roxburghii*. In addition, two glucoside compounds, (2*S*) 1-thio-*β*-D-glucopyranose-*N*-(sulfooxy)-2-hydroxymethylbutylisothiocyanate (glucocleomine, **4**) and (2*S*) 1-thio-*β*-D-glucopyranose-*N*-(sulfooxy)-2-methylbutylisothiocyanate (**5**) were identified from the seeds and from the volatile hydrolysis product from kernels (Fig. 2) (Kjaer and Friis, 1962, Kjaer and Thomson, 1962). In the years that followed, a number of new and known compounds were isolated from this species, but realistically, chemical research on African species did not start before 1997.

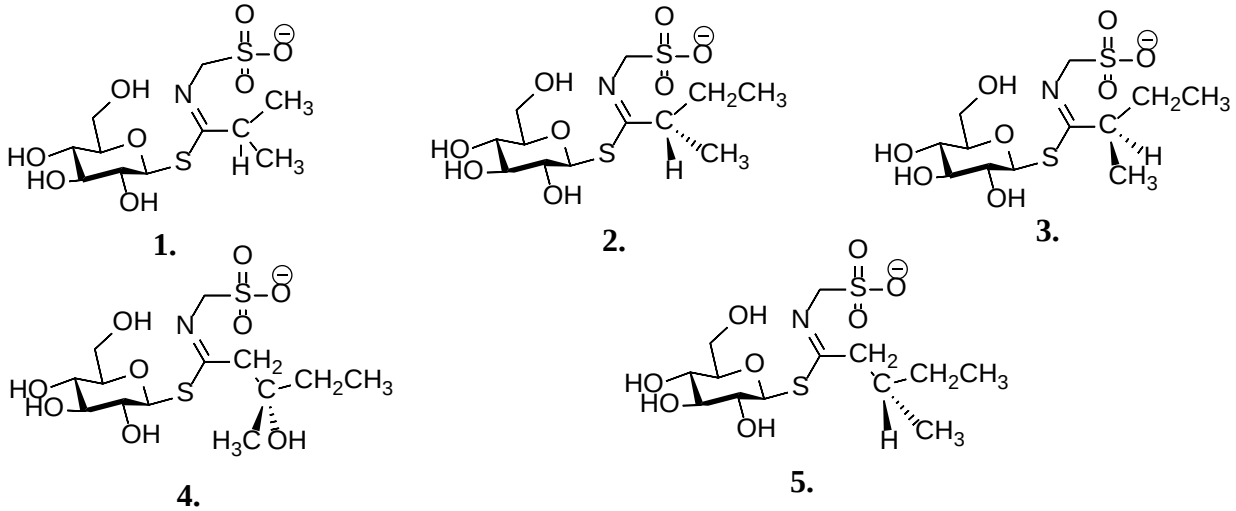
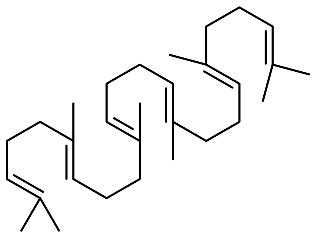


Figure 2. Structures of compounds **1**-**5**

In the meantime, nineteen African and Asian species have been investigated providing a total of 142 compounds, belonging to various classes of secondary metabolites.

3.2.1. Triterpenoids

Three main classes of triterpenoids were isolated from this genus: one linear triterpenoid, squalene (**6**), from the leaves of *D. hieranensis* Hayata (Pax & K. Hoffm.) (Chen, 1999) as well as in huge quantities from the leaves and stems of *D. cumingii* Baill. (Pax & K. Hoffm.) (Sun, 2014); one tetracyclic triterpenoid, 3*β*-acetoxycycloart-24-en-23-one (**7**) reported from the leaves of *D. roxburghii* (Mukherjee, 2012) (Fig. 3); and five subclasses of pentacyclic triterpenoids (friedelane, oleanane, lupane, hopane and adianane).



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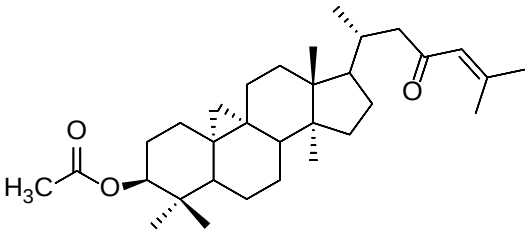

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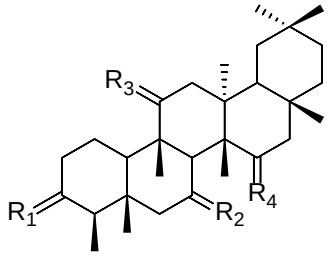
Figure 3. Structures of compounds **6** and **7**

3.2.1.1. Pentacyclic triterpenoids

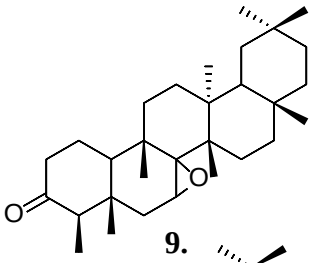
3.2.1.1.1. Friedelane

The first friedelane (Fig. 4) isolated from this genus was putanjivadione (**8**) from the trunk bark of the Asian *D. roxburghii* (Garg and Mitra, 1968b) and it was shown to be friedelane-3,7-dione (Sengupta and Chakraborty, 1968). Subsequently, the compound was re-isolated from the African species *D. gossweileri* (Sow *et al.*, 1994; Ngouela *et al.*, 2003; Wandji *et al.*, 2003); *D. molunduana* Pax. & K. Hoffm. (Wandji *et al.*, 2000); *D. chevalieri* (Wansi *et al.*, 2006, 2007); *D. gerrardii* (Ng´ang´a *et al.*, 2008); *D. laciniata* Pax. (Hutch.) (Fannang *et al.*, 2011); the Asian *D. hainanensis* Merr. (Chen *et al.*, 2014) as well as from *D. roxburghii* (Sengupta and Mukherjee, 1968; Chopra *et al.*, 1970b, Mukherjee *et al.*, 2012). The synthetic compound 7,8-epoxyfriedelane (**9**) was produced by a series of chemical reactions from putranjivadione (**8**) (Dey and Banerjee, 1995). Three isomers of this compound, drypemolundein B (**10**), 3-oxofriedelan-25-al (**11**) and 3,15-dioxofriedelane (**12**) were isolated from eight Cameroonian species: *D. molunduana*, *D. gossweileri* (Wandji *et al.*, 2000, 2003), *D. chevalieri* (Wansi *et al.*, 2007), *D. parvifolia* (Müll. Arg.) Pax. & K. Hoffm. (Nenkep *et al.*, 2008), *D. tessmanniana* Pax. (Pax. & K. Hoffm.) (Dongfack *et al.*, 2008), *D. paxii* Hutch. (Chiozem *et al.*, 2009), *D. inaequalis* Hutch. (Awanchiri *et al.*, 2009) and *D. laciniata* (Fannang *et al.*, 2011). Friedelin (**13)**, a compound originally described from cork by Chevreul in 1807, was reported from the two Asian species *D. roxburghii* (Garg and Mitra, 1968b; Sengupta and Mukherjee, 1968; Chopra *et al.*, 1970b; Mukherjee et al., 2012) and *D. hainanensis* (Chen *et al.*, 2014) and, in the following as

well from the African species *D. gossweileri* (Sow et al., 1994; Ngouela *et al.*, 2003, Wandji *et al.*, 2003), *D. littoralis* (C. B. Rob.) Merr. (Lin *et al.*, 2001), *D. chevalieri* (Wansi *et al.*, 2006, 2007), *D. gerrardii* (Ng´ang´a *et al.*, 2008, 2012), *D. parvifolia* (Nenkep *et al.*, 2008), *D. tessmanniana* (Dongfack *et al.*, 2008), *D. paxii* (Chiozem *et al.*, 2009), *D. inaequalis* (Awanchiri *et al.*, 2009), and *D. laciniata* (Fannang *et al.*, 2011). Its isomer friedelan-7-one (**14**) was isolated from *D. paxii* (Chiozem *et al.*, 2009). Two trioxofriedelanes, 3,6-dioxo-D:A-friedo-oleanan-24-al (**15**) and 3*β*-hydroxyfriedelane-7,12,22-trione (**16**) were isolated from *D. chevalieri* (Wansi *et al.*, 2007) and *D. laciniata* (Fannang *et al.*, 2011), respectively. Furthermore, friedelan-3*β*-ol (**17**), its stereoisomer epifriedelanol (**18**), epifriedelanol methyl ether (**19**) and 5*β*,24-cyclofriedelan-3-one (**20**) were isolated from *D. amoracia* (Wandji *et al.*, 2003), *D. tessmanniana* (Dongfack *et al.*, 2008) and *D. gerrardii* (Ng´ang´a et al., 2008, 2012; Hata et al., 2014). Friedelane-3*α*,16*β*-diol (**21**), its isomer friedelane-3*β*,29*β*-diol (**22**) and the oxydized isomer 3-oxo-friedelan-29-ol (**23**) were reported from *D. hieranensis* and *D. congestiflora* Chuin & T. Chen. (Chen *et al.*, 1999, Chen, 2015). Furthermore, from the Camerooninan species *D. paxii* and *D. inaequalis* as well as the two Asian species *D. hoanensis* Gagnep. and *D. roxburghii*, four compounds were isolated, namely 12*α*-hydroxyfriedelane-3,15-dione (**24**), 3*β*-hydroxyfriedelan-25-al (**25**), 3*α*-hydroxyfriedelan-7-one (**26**), 3*α*-hydroxyfriedelan-12-one (**27**), 3*α*-hydroxyfriedelan-25-al (**28**) and roxburghonic acid or 3-ketofriedelan-25-oic acid (**29**) (Garg and Mitra, 1968b, 1971a; Awanchiri *et al*., 2009; Chiozem *et al.*, 2009; Wittalai *et al.*, 2014). Four *seco*-friedelane, putanjivic acid or 3,4-sec-friedelan-4(23)-en-3-oic acid (**30**), methylputranjivate (**31**), putranjic (putric) acid or 2-hydroxy-3,4-seco-D:A-friedooleanan-3-oic acid (**32**) and methylputranjate (**33**) were isolated from *D. roxburghii* (Garg and Mitra, 1968b, 1969; Chopra *et al.*, 1968, 1970a; Aojagi *et al.*, 1973). Five *nor*-friedelane, hainanenone or 4-hydroxy-23-*nor*-friedel-3-one (**34**), hainanenone A or 23-*nor*-friedel-3-one (**35**), putrone or 3-oxo-25-*nor*-friedel-9(11)-ene (**36**), putrol or 3*α*-hydroxy-25-*nor*-friedel-9(11)ene (**37**) and putralone or 10*α*-hydroxy-25-*nor* D:A friedo-olean-9(11)-en-3-one (**38**) were isolated from *D. hainanensis* (Chen *et al.*, 2014; He *et al.*, 2015) and *D. roxburghii* (Chopra *et al.*, 1968; Aiyar *et al.*, 1973; Mukherjee *et al.*, 2012). The suggested structure of **36** was supported by its conversion into *D*:*A*-friedo-oleana-7,9 (11)-diene, and it was also reported to have been synthesized from 25-acetoxy-*D*:*A*-friedo-olean-7-ene (Sengupta *et al.*, 1979). The compounds 3*α*-(*E*)-caffeoyloxyfriedelan-7-one (**39**) and 3*α*-(*E*)-*p*-coumaroyloxyfriedelan-7-one (**40**) were isolated from the DCM extract of the roots of *D. hoanensis* (Wittalai *et al.*, 2014).



8. $R_1 = R_2 = O$; $R_3 = R_4 = H_2$
10. $R_1 = R_3 = O$; $R_2 = R_4 = H_2$
12. $R_1 = R_4 = O$; $R_2 = R_3 = H_2$
13. $R_1 = O$; $R_2 = R_3 = R_4 = H_2$
14. $R_1 = R_3 = R_4 = H_2$; $R_2 = O$



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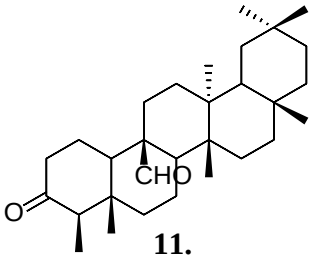

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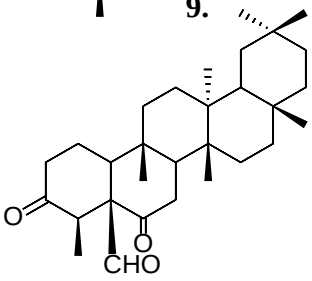

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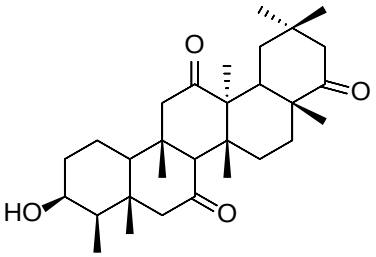

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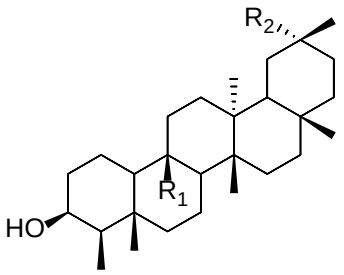
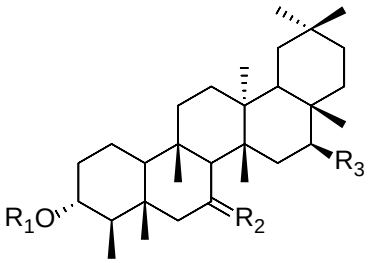
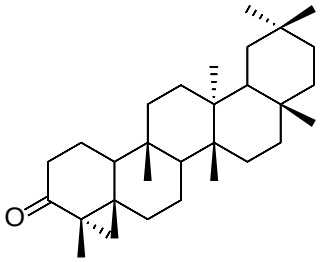


17. $R_1 = R_2 = CH_3$
22. $R_1 = CH_3$; $R_2 = CH_2OH$
25. $R_1 = CHO$; $R_2 = CH_3$



18. $R_1 = H$; $R_2 = H_2$; $R_3 = H$
19. $R_1 = CH_3$; $R_2 = H_2$; $R_3 = H$
21. $R_1 = H$; $R_2 = H_2$; $R_3 = OH$
26. $R_1 = H$; $R_2 = O$; $R_3 = H$



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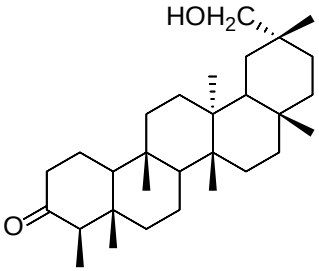

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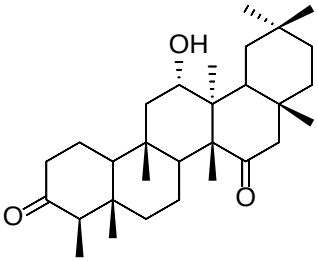

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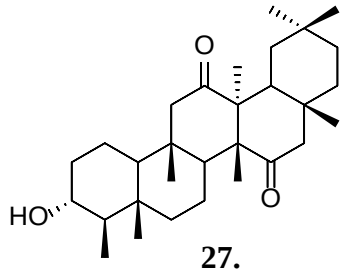

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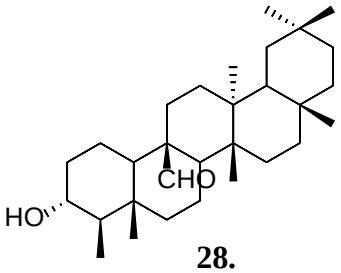

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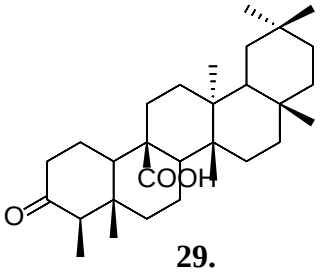

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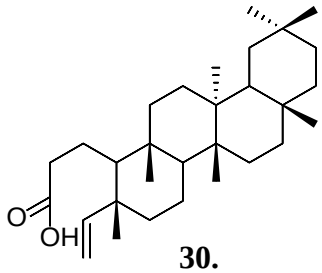

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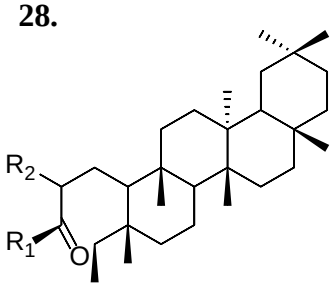
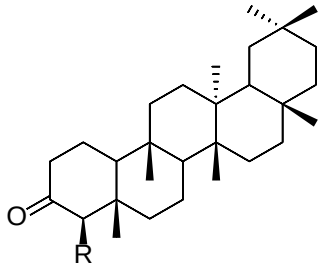
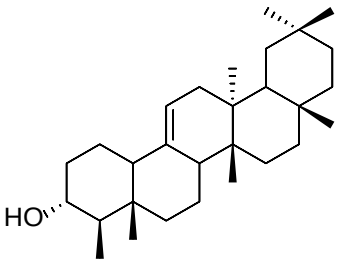


31. R_1 = OCH_3; R_2 = H
32. R_1 = R_2 = OH
33. R_1 = OCH_3; R_2 = OH



34. R = OH
35. R = H



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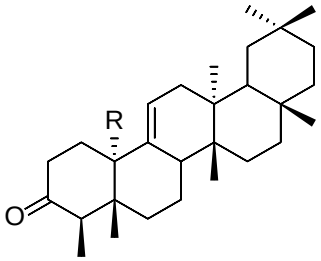
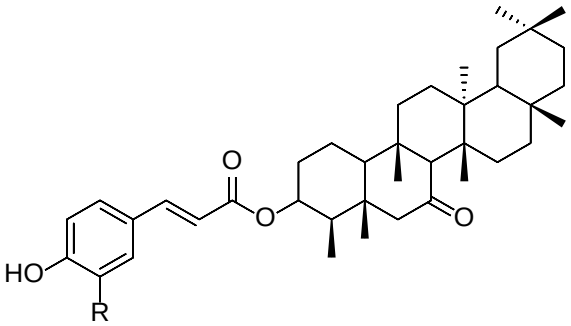


36. R = H
38. R = OH



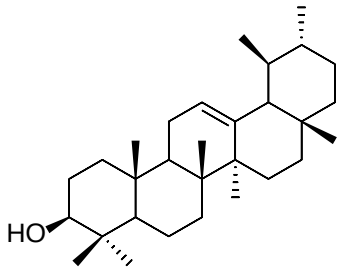
39. R = OH
40. R = H

Figure 4. Structures of compounds **8**-**40**

3.2.1.1.2. Oleanane

The isolated oleananes (Fig. 5) of this genus belong to the class of olean-12-ene. From the EtOH extract of the stems of *D. littoralis*, *α*-amyrin (**41**) was reported (Lin *et al.*, 2001), as well as from the

EtOH extract of leaves and stems of *D. hainanensis* (Chen *et al.*, 2014). Its isomer *β*-amyrin (**42**) was also obtained from the DCM-MeOH (1/1) extract of the stem of *D. chevalieri* (Wansi *et al.*, 2007); the leaves of *D. roxburghii* (Badole *et al.*, 2011); and the EtOH extract of leaves and stems of *D. hainanensis* (Chen *et al.*, 2014). Furthermore, *β*-amyrone (**43**) was isolated from the MeOH extract of the stem bark of *D. gossweileri.* In addition, erythrodiol (**44**), bayogenin acid (**45**), hederagenin (**46**) and 3*β*-acetoxyolean-12-en-28-oic acid (**47**) were isolated from the DCM-MeOH (1:1) stem extract of *D. molunduana* (Wandji *et al.*, 2000). Erythrodiol (**44**) and oleanolic acid (**48**) were also reported to be obtained from the DCM-MeOH (1:1) extract of *D. chevalieri* (Wansi *et al.*, 2006, 2007) and the leaves of *D. roxburghii* (Mukherjee *et al.*, 2012). *D. gossweileri* contained maslinic acid (**49**) (Sow *et al.*, 1994). The air-dried stems and ripe fruit of *D. inaequalis* provided the 28*β*-D-glucopyranosyl-30-methyl-3*β*-hydroxyolean-12-en-28,30-dioate (**50**) along with serjanic acid (**51**), 28*β*-D-glucopyranosyl-3*β*-hydroxyolean-12-en-28-oate (**52**), serratagenic acid (**53**) and queretaroic acid (**54**) (Awanchiri *et al.*, 2009). From the MeOH extract of the whole stem of *D. laciniata*, the known compounds oleanolic acid (**48**), 3*β*,22*β*-dihydroxyolean-12-en-28-oic acid (**55**), and chikusetsusaponin IVa methyl ester (**56**) were isolated. Furthermore, the EtOH/H_2O (95/5) extract of the twigs and leaves of *D. perreticulata* contained collinsogenin (**57**) (Ge *et al.*, 2014). A crystalline triterpenoid saponin named putranjivoside (**58**) was isolated from the seed coat of *D. roxburghii* and was established to be 3*β*-L-arabino-L-rhamno-D-glucoside of oleanolic acid (Garg and Mitra, 1968a). Furthermore, the benzene extract of the leaves of *D. roxburghii* gave *β*-amyrin (**42**) and a *β*-amyrin palmitate (**59**) (Chopra *et al.*, 1968). The DCM-MeOH (1:1) extract of the stem of *D. chevalieri* afforded a triterpenoid named drypechevalin A or 11-oxo-*β*-amyrin-3*β*-ylcaffeate (**60**) (Wansi *et al.*, 2006). From the MeOH extract of the stem bark of *D. tessmanniana*, a 3*β*-*O*-(*E*)-3,5-dihydroxycinnamoyl-11-oxo-olean-12-ene (**61**) was reported (Dongfack *et al.*, 2008). From the DCM-MeOH (1:1) extract of the leaves of *D. gerrardii*, the saponin putranoside A (**62**) was isolated (Hata *et al.*, 2014).



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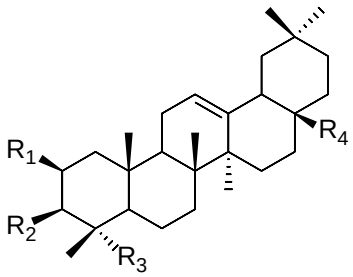
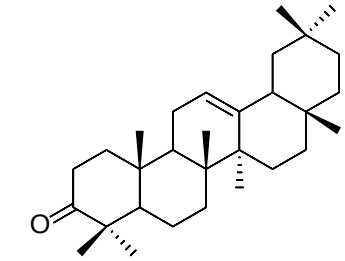


42. R_1 = H; R_2 = OH; R_3 = R_4 = CH_3
44. R_1 = H; R_2 = OH; R_3 = CH_3; R_4 = CH_2OH
45. R_1 = R_2 = OH; R_3 = CH_2OH; R_4 = COOH
46. R_1 = H; R_2 = OH; R_3 = CH_2OH; R_4 = COOH
47. R_1 = H; R_2 = OAc; R_3 = CH_3; R_4 = CH_2OH
48. R_1 = H; R_2 = OH; R_3 = CH_3; R_4 = CH_2OH



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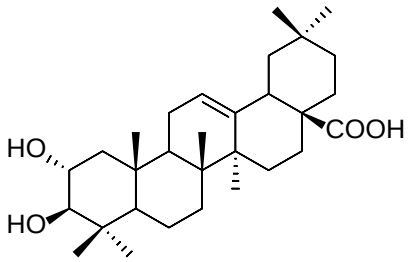

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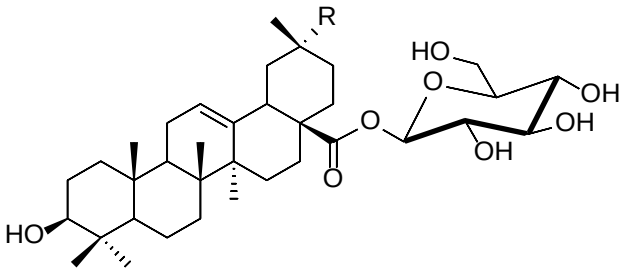
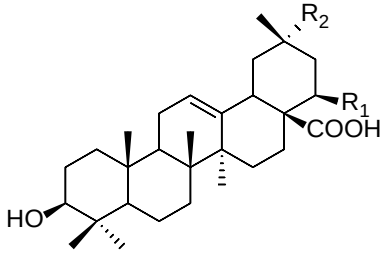
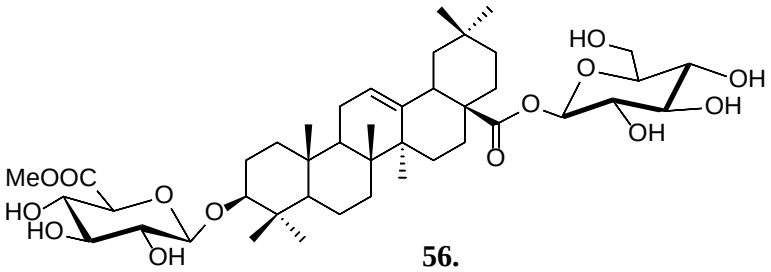


50. R = $COOCH_3$
52. R = CH_3



51. R_1 = H; R_2 = $COOCH_3$
53. R_1 = H; R_2 = COOH
54. R_1 = H; R_2 = CH_2OH
55. R_1 = OH; R_2 = CH_3



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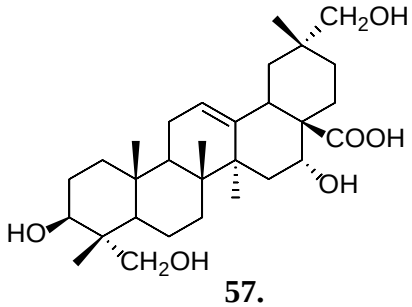

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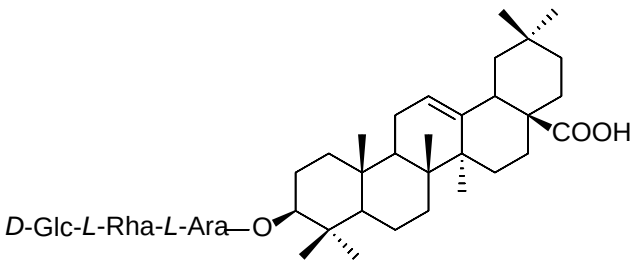

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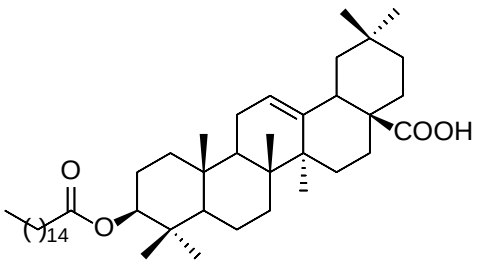

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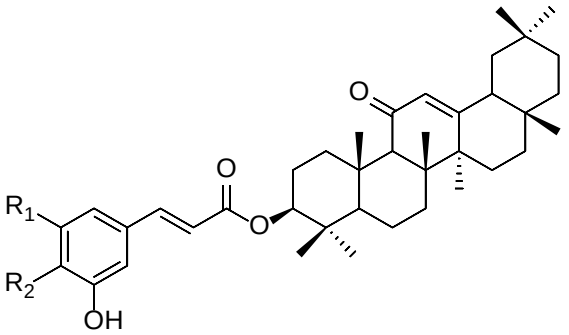
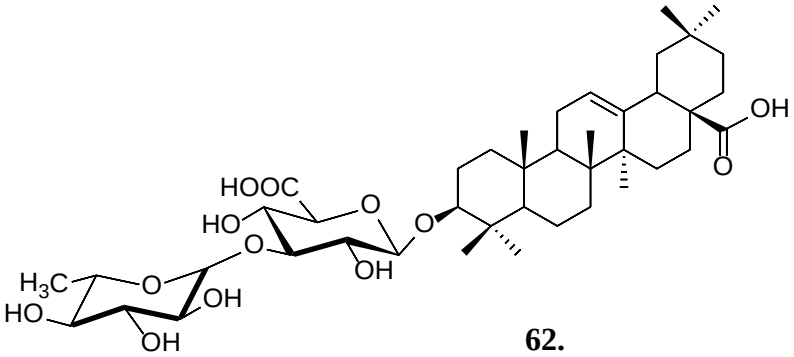


60. R_1 = **H;** R_2 = **OH**
61. R_1 = **OH;** R_2 = **H**



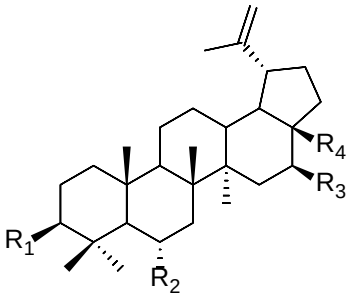
62.

Figure 5. Structures of compounds **41**-**62**

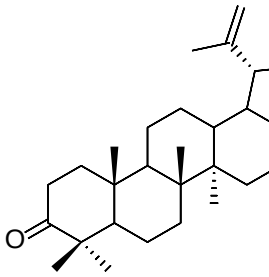
3.2.1.1.3. Lupane

The DMC-MeOH (1:1) extract of the stem of *D. chevalieri* afforded lupeol (**63**) (Wansi *et al.*, 2006; 2007), which was subsequently also reported from the MeOH extract of the stem bark of *D. tessmanniana* (Dongfack *et al.*, 2008), and the EtOH extract of leaves and stems of *D. hainanensis* (Chen *et al.*, 2014) (Fig. 6). Furthermore, the DCM-MeOH (1:1) extract of the stems of *D. chevalieri* afforded lupeone **64** (Wansi *et al.*, 2006), and the air-dried 95% EtOH/H_2O extract of the stems of *D. congestiflora* delivered betulinic acid (**65**) (Chen *et al.*, 2015). In addition, the crude ethyl acetate and DCM extracts of the stem of *D. gerrardii* delivered resinone (**66**) (Ng'ang'a *et al.*, 2011, 2012). The stems and ripe fruit of *D. inaequalis* afforded lup-20(29)-en-3*β*,6*α*-diol (**67**) and 3*β*-acetoxylup-20(29)-en-6*α*-ol (**68**) (Awanchiri *et al.*, 2009). From the MeOH extract of the stem bark of *D. tessmanniana*, 3*β*,6*α*-dihydroxylup-20(29)-en (**69**) was isolated (Dongfack *et al.*, 2008). From twigs and leaves of *D. perreticulata* extracted with EtOH/H_2O (95/5) messagenic acid D (**70**) and G (**71**), betulonic acid (**72**), 2*α*,3*α*-dihydroxy-lup-20(29)-en-28-oic acid (**73**), nor-29-lupane and platanic acid (**74**) were isolated (Ge *et al.*, 2014). Platanic acid (**74**) was as well isolated from the air-dried 95% EtOH/H_2O extract of the stems of *D. congestiflora* (Chen *et al.*, 2015). Furthermore, four caeffeoyllupane derivatives were isolated from this genus, namely 3*β*-caffeoylbetulinic acid (**75**) from

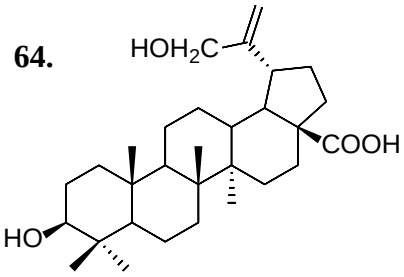
the stems of *D. congestiflora* (Chen *et al.*, 2015), 3*β*-caffeoyloxylup-20(29)-en-6*α*-ol (**76**) from the air-dried stems and ripe fruit of *D. inaequalis* (Awanchiri *et al.*, 2009) and two isomers betulin-3*β*-(*Z*)-caffeate (**77**) and betulin-3*β*-(*E*)-caffeate (**78**) from twigs and leaves of *D. perreticulata* Gagnep. (Ge *et al.*, 2014).



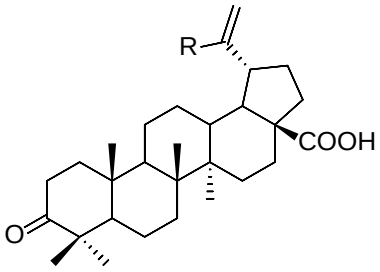
63. R_1 = OH; R_2 = R_3 = H; R_4 = CH_3
65. R_1 = OH; R_2 = R_3 = H; R_4 = COOH
66. R_1 = OH; R_2 = H; R_3 = OH; R_4 = CH_3
67. R_1 = OH; R_2 = OH; R_3 = H; R_4 = CH_3
68. R_1 = OAc; R_2 = OH; R_3 = H; R_4 = CH_3
69. R_1 = OH; R_2 = OH; R_3 = H; R_4 = COOH



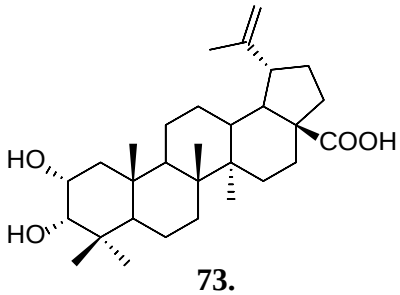
64.



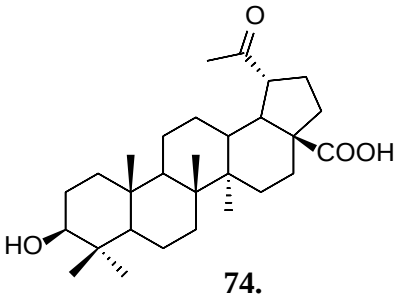
70.



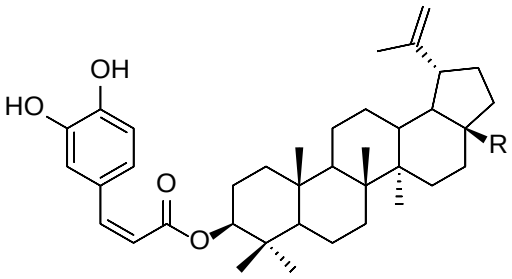
71. R = CH_2OH
72. R = CH_3



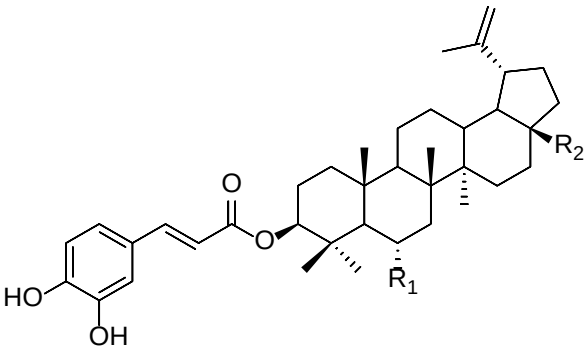
73.



74.



75. R = CH_2OH
77. R = COOH

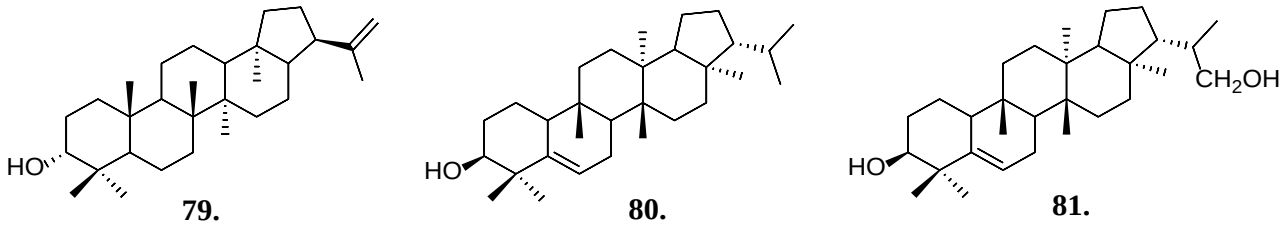


76. R_1 = OH; R_2 = CH_3
78. R_1 = H; R_2 = COOH

Figure 6. Structures of compounds **63**-**78**

3.2.1.1.4. Hopane and adianane

The EtOAc and DCM extracts of the stem of *D. gerrardii* afforded 3*β*-epimoretenol (**79**) (Ng'ang'a *et al.*, 2008, 2012), while the leaves of *D. roxburghii* revealed two adiananes, namely 3*β*-acetoxyadiane-5-ene (**80**) and adian-5-en-3*β*,29-diol (**81**) (Mukherjee *et al.*, 2012) (Fig. 7).

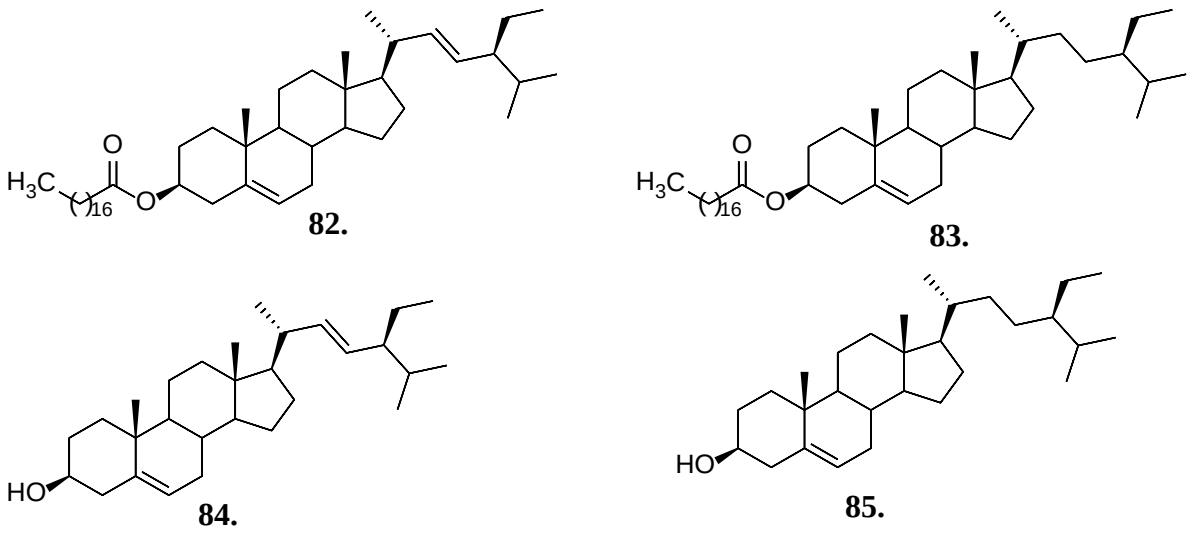


79. **80.** **81.**

Figure 7. Structures of compounds **79**-**81**

3.2.2. Steroids

Seven stigmastane-type steroids were isolated from this genus (Fig. 8). Stigmasterol stearate (**82**), *β*-sitosterol stearate (**83**), stigmasterol (**84**) and *β*-sitosterol (**85**) were reported from the bark of *D. gossweileri* (Dupont *et al.*, 1997). Stigmasterol (**84**), *β*-sitosterol (**85**) and their glycosylated derivatives 3-*O*-*β*-D-glucopyranosylstigmasterol (**86**) and 3-*O*-*β*-D-glucopyranosyl-*β*-sitosterol (**87**) were isolated from the leaves of *D. hieranensis* (Chen *et al.*, 1999), the stem bark of *D. parvifolia* (Nenkep *et al.*, 2008), the stem bark of *D. tessmanniana* (Dongfack *et al.*, 2008), the stems of *D. gerrardii* (Ng'ang'a *et al.*, 2008), the stems of *D. paxii* (Chiozem *et al.*, 2009), the stems and ripe fruit of *D. inaequalis* (Awanchiri *et al.*, 2009), the whole stem of *D. laciniata* (Fannang *et al.*, 2011) and the leaves and stems of *D. hainanensis* (Chen *et al.*, 2014). Furthermore, 3*β*-hydroxysigmasta-5,22-dien-7-one (**88**) was isolated from the DCM extract of the roots of *D. hoaensis* (Wittayalai *et al.*, 2014).



82. **83.**

84. **85.**

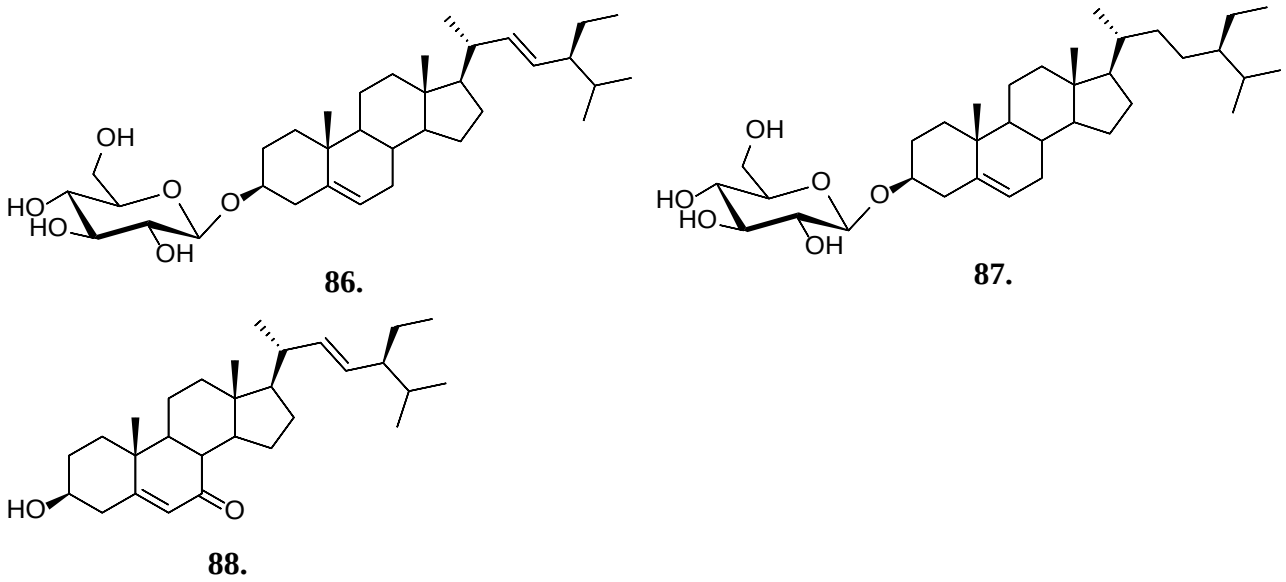
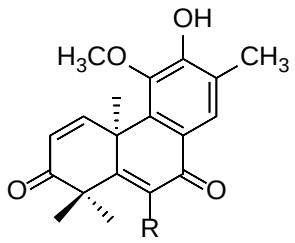


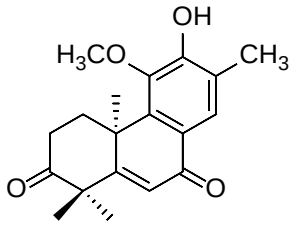
Figure 8. Structures of compounds **82-88**

3.2.3. Diterpenes

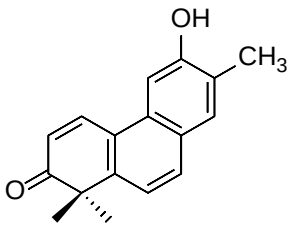
Ten dinorditerpenoids belonging to the pimarane class with the armoratic ring C, were reported from this genus (Fig. 9). Chemical investigation of the EtOH extract of the stem of *D. littoralis* yielded three tricyclic diterpenes namely drypetenone A or 10*S*-12-hydroxy-11-methoxy-13-methylpodocarpa-1,5,8,11,13-pentaene-3,7-dione (**89**), drypetenone B or 10*S*-12-hydroxy-11-methoxy-13-methylpodocarpa-5,8,11,13-tetraene-3,7-dione (**90**), and drypetenone C or 10*S*-12-hydroxy-6,11-dimethoxy-13-methylpodocarpa-1,5,8,11,13-pentaene-3,7-dione (**91**) (Lin *et al.*, 2001). In addition, from the DCM-MeOH (1:1) stem extract of *D. gerrardii*, a phenanthrenone derivative, drypetenone D (**92**), and a phenanthrenone heterodimer, drypetenone E (**93**) were isolated (Hata *et al.*, 2014). Furthermore, a podocarpane derivative named gossweilone or 6,12-dihydroxy-13-methylpodocarpa-5,8,11,13-tetraene-3,7-dione (**94**) was isolated from the MeOH stem bark extract of *D. gossweileri* (Ngouela *et al.*, 2003). The twigs and leaves of *D. perreticulata* extracted with EtOH/H_2O (95/5) afforded dryperrein A or (10*S*)-11,12-dihydroxy-6-methoxy-15,16-dinorpimara-5,8,11,13-tetraene-3,7-dione (**95**), dryperrein B or (10*S*)-6,11,12-trihydroxy-15,16-dinorpimara-5,8,11,13-tetraene-3,7-dione (**96**), dryperrein C or (10*S*)-11,12-dihydroxy-6-methoxy-15,16-dinorpimara-1,5,8,11,13-pentaene-3,7-dione (**97**), and dryperrein D or (10*S*)-6,11,12-trihydroxy-15,16-dinorpimara-1,5,8,11,13-pentaene-3,7-dione (**98**) (Ge *et al.*, 2014).



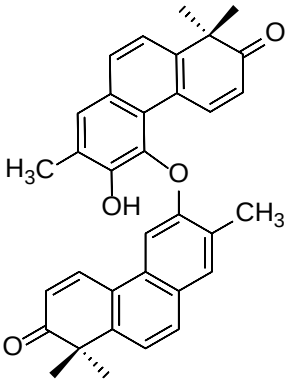
89. R = H
91. R = OCH_3



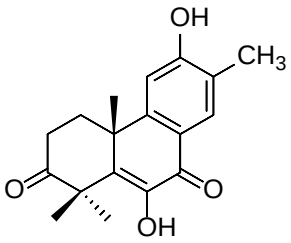
90.



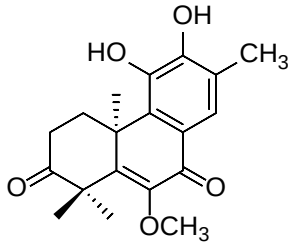
92.



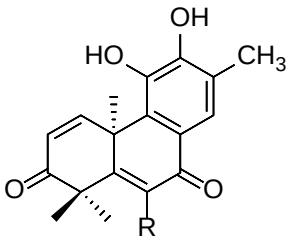
93.



94.



95.



96. R = H
97. R = OCH_3
98. R = OCH_3

Figure 9. Structures of compounds **89**-**98**

3.2.4. Sesquiterpenes

The first sesquiterpene isolated from the genus was drypemolundein A (**99**) (Fig. 10), which was from the DCM/MeOH (1:1) extract of the stem of *D. molunduana* (Wandji *et al.*, 2000). This sesquiterpene with the original structure did not follow the isoprenyl rule, since its structure contains two units of isoprenyl and one linear pentane. Furthermore, eight eremophilane sesquiterpenes were isolated, namely furanoeudesm-1-on-13-oic acid (**100**) from the stem of *D. chevalieri* (Wansi *et al.*, 2007), 1α-hydroxyeremophila-6,9,11-trien-8-one (**101**) and 4α-hydroxyeremophila-1,9-diene-3,8-dione (**102**) from the stems of *D. congestiflora* (Chen *et al.*, 2015), as well as hoaensibenzofuranal (**103**),

hoaensieudesone (**104**), hoaensifuranonal (**105**), hoaensieremodione (**106**), hoaensieremone (**107**) and the known compound warburgin (**108**) from the the roots of *D. hoaensis* (Wittalajai *et al.*, 2014). A linear sesquiterpene alcohol, nerolidol (**109**) was isolated from leaves and stems of *D. cumingii* (Sun *et al.*, 2014).

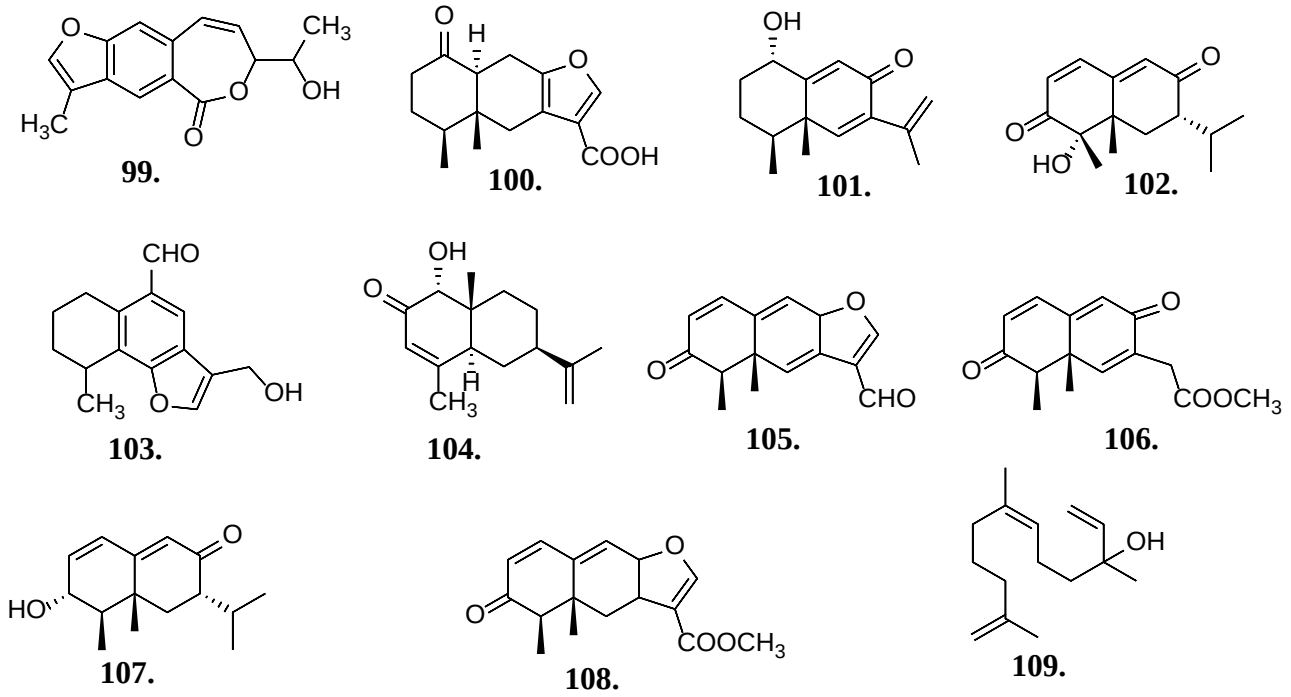


Figure 10. Structures of compounds **99**-**109**

3.2.5. Phenylpropanoids and phenylethanoid

Syringin methyl ether (**110**) was the first phenyl propanoid glycoside reported from this genus (Fig. 11), and was isolated from *D. roxburghii* (Sipahimalani *et al.*, 1994). Furthermore, phenylpronanoid glycoside named drypearmoracein A or (*E*)-4,5,6,7-tetrahydroxy-2-benzylhept-2-enoic acid (**111**) was reported from the MeOH stem bark extract of *D. amoracia* (Wandji *et al.*, 2003). Phytochemical investigation of *D. hainanensis* resulted in the isolation of three phenylpropanoids named drypetesins A-C (**112**-**114**) (Zhang *et al*., 2015). From the DCM extract of the roots of *D. hoanensis* as well as the ethanolic extract of the stem of *D. littoralis*, coniferaldehyde or 4-hydroxy-3-methoxycinnamaldehyde (**115**), sinapaldyehde or 4-hydroxy-3,5-dimethoxycinnamaldehyde (**116**) and 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (**117**) were reported (Lin *et al*., 2001, Wittayalai *et al*., 2014). In addition, the phenylethanoid *N*-*β*-glucopyranosyl-*p*-hydroxyphenylacetamide (**118**) was isolated from the MeOH extract of the bark of *D. gossweileri* (Matochko, 2010, Ata *et al.*, 2011).

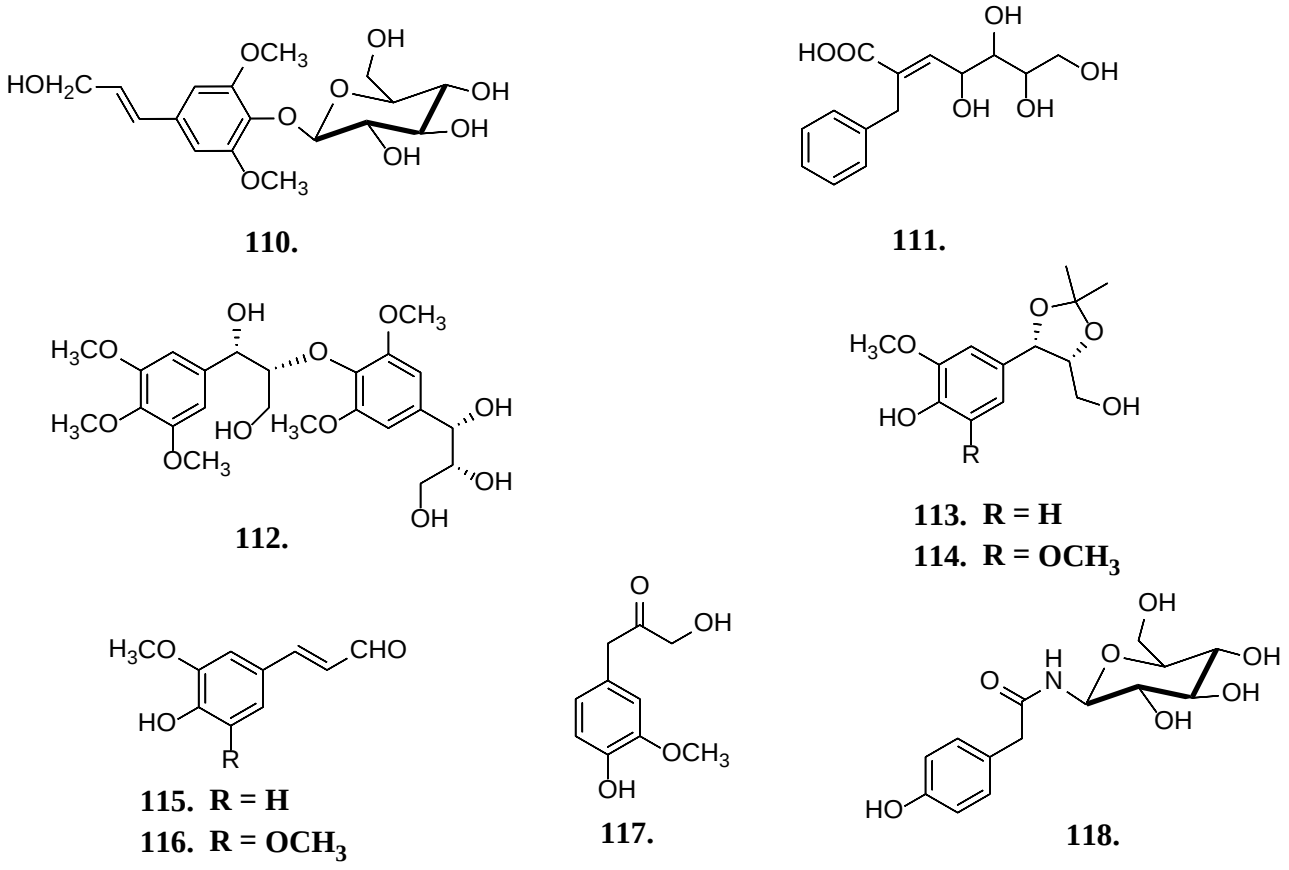


Figure 11. Structures of compounds **110**-**118**

3.2.6. Lignanes

The MeOH extract of the leaves of *D. roxburghii* revealed (+)-syringaresinol-4'-*O*-*β*-D-glucopyranoside (**119**), (-)-syringaresinol-4',4''-*O*-*β*-D-diglucopyranoside (**120**) and (-)-pinoresinol-4'-*O*-*β*-D-glucopyranoside (**121**) (Sipahimalani *et al.*, 1994). In addition, (-)-syringaresinol (**122**) reported from the DCM/MeOH (1:1) extract of the stem of *D. molunduana* (Wandji *et al.*, 2000) was as well isolated from the ethanolic extract of the stem of *D. littoralis* (Lin *et al.*, 2001) and the DCM extract of the roots of *D. hoaensis* (Wittayalai *et al.*, 2014). Furthermore, smilaside C (**123**) was isolated from the DCM extract of the roots of *D. hoaensis* (Wittayalai *et al.*, 2014), and the ethanolic extract of the stem of *D. littoralis* gave lariciresinol (**124**), the neolignan boehmenan (**125**), and the neolignan boehmenan D (**126**) (Lin *et al.*, 2001) (Fig. 12).

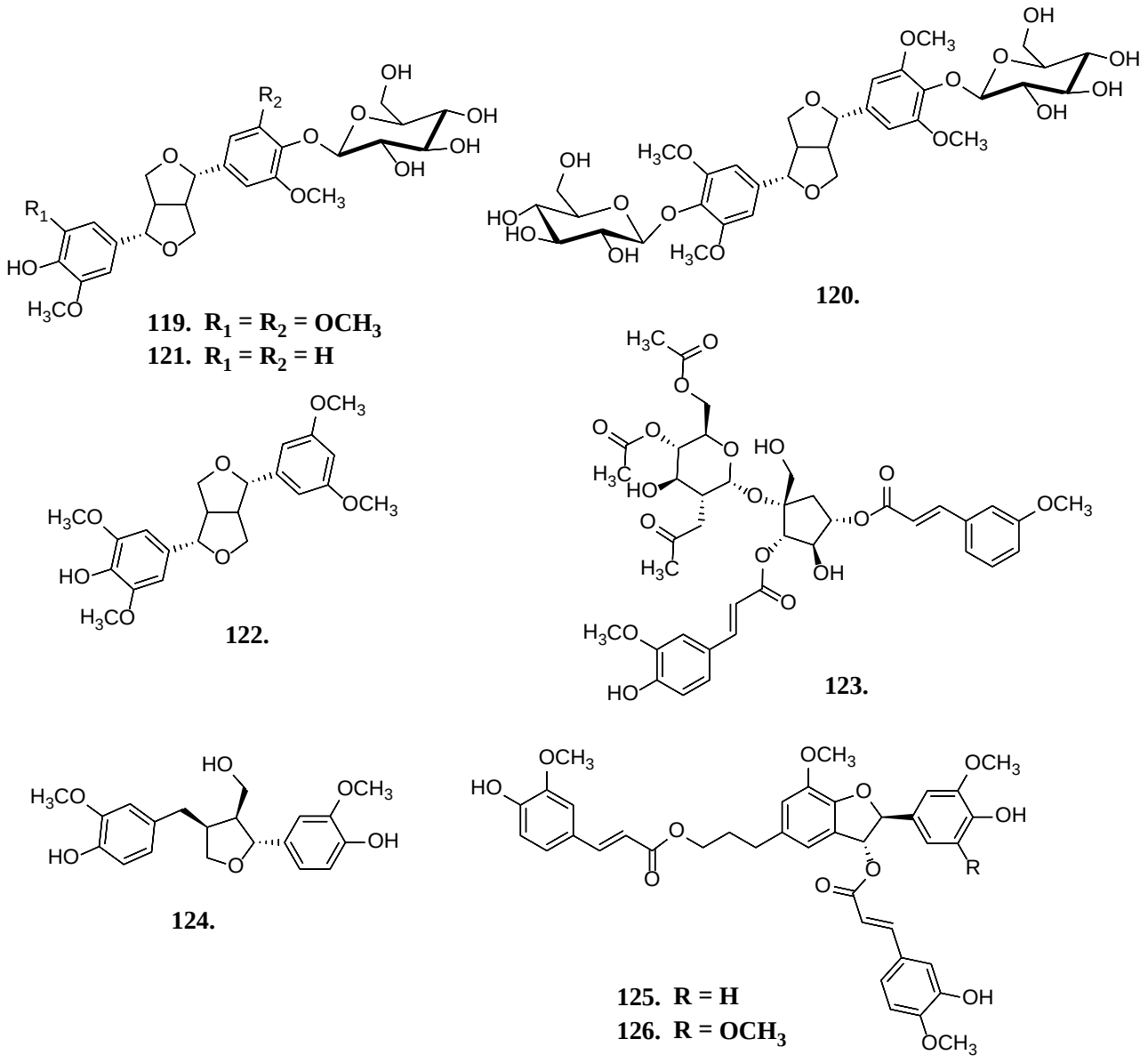
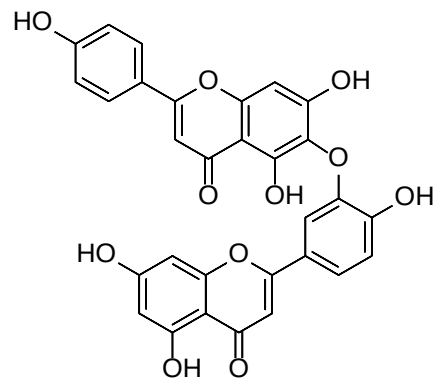


Figure 12. Structures of compounds **119**-**126**

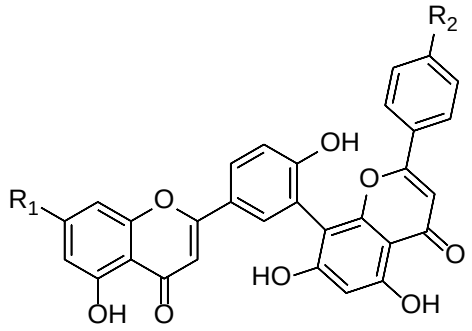
3.2.7. Flavonoids, xanthone and anthraquinone

From the crude extract of *D. gerrardii*, drypetdimer A (**127**) was isolated (Ng'ang'a *et al*., 2011) (Fig. 13), while the DCM extract of the stem contained amentoflavone (**128**) (Ng'ang'a *et al.*, 2012). The latter was previously reported from the EtOH extract of the stem of *D. littoralis* (Lin *et al*., 2001). Furthermore, the extract of the stem bark of *D. parvifolia* delivered a flavan glycoside, 7-hydroxy-5-*O*-*β*-D-glucopyranosideflavan (**129**), and an unusual chalcone glycoside, (*Z*)-4´,6´-dihydroxy-2´-*O*-*β*-D-glucopyranosidechalcone (**130**) (Nenkep *et al*., 2008), while the EtOH extract of fresh leaves of *D. roxburghii* yielded gallocatechin (**131**) (Chopra et *al*., 1970b). In addition, a biflavonoid, namely putraflavone or 7,4‴-dimethyl amentoflavone (**132**), was isolated from the acidic fraction of the alcoholic extract of the leaves of this plant (Garg and Mitra, 1971b). Finally, xanthone 1-hydroxy-7-hydroxymethyl-6-methoxyxanthone (**133**) and anthraquinone drypearmoracein B or 2,3-dihydroxy-

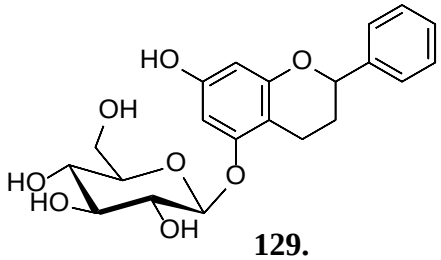
9,10-tetrahydroanthra-1,4-quinone (**134**) were reported from the stem of *D. littoralis* (Lin *et al*., 2001), respectively, from the MeOH extract of the stem bark of *D. armoracia* (Wandji *et al*., 2003).



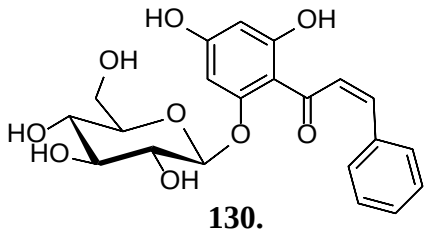
127.



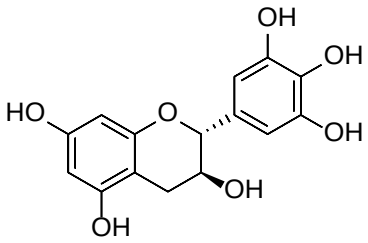
128. $R_1 = R_2 = OH$
132. $R_1 = R_2 = OCH_3$



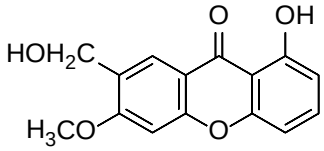
129.



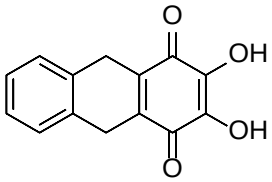
130.



131.



133.

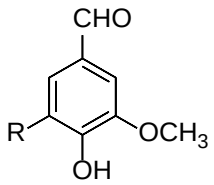


134.

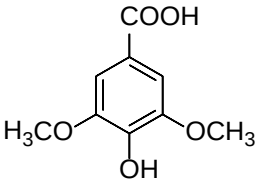
Figure 13. Structures of compounds **127**-**134**

3.2.8. Other metabolites

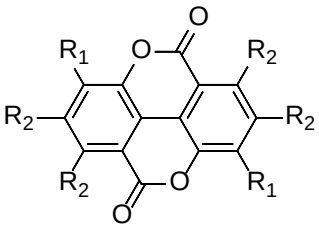
The DCM extract of the roots of *D. hoaensis* afforded vanillin (**135**) and syringaldehyde (**136**) (Wittayalai *et al*., 2014). Furthermore, the EtOH extract of fresh leaves of *D. roxburghii* yielded gallic acid (**137**) and ellagic acid (**138**) (Chopra *et al*., 1970b), while the $CHCl_3$-soluble fraction of the leaves of *D. hieranensis* afforded the known tannin hexamethoxyellagic acid (**139**) (Chen *et al*., 1999) (Fig. 14).



135. R = H
136. R = OMe



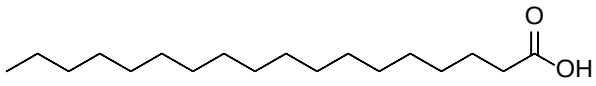
137.



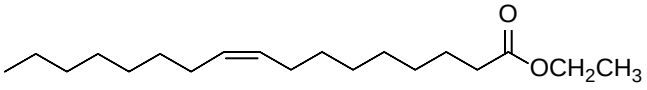
138. R_1 = H, R_2 = OH
139. R_1 = R_2 = OCH_3

Figure 14. Structures of compounds **135-139**

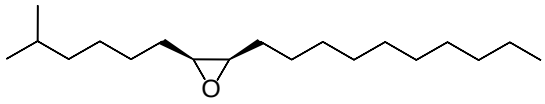
Furthermore, stearic acid (**140**) reported from the bark of *D. gossweileri* (Dupont *et al*., 1997). In addition, two liposoluble constituents from the leaves and stems of *D. cumingii* afforded the fatty acid ethyl ester ethyl oleate (**141**) and disparlure or 2-methyl-7*R*,8*S*-epoxy-octadecane (**142**), also a pheromone of the gypsy moth (Sun *et al*., 2014) (Fig. 15).



140.



141.



142.

Figure 15. Structures of compounds **140-142**

From *D. roxburghii* seeds, a multifunctional ~12 kDa heterodimeric protein named putrin belonging to 2*S* albumin family was purified, characterised and cloned (Tomar *et al.*, 2014). In addition, a highly stable trypsin inhibitor was isolated from the seeds of *D. roxburghii.* The protein consists of a single polypeptide chain of 34 kDa and inhibits bovine trypsin in 1:1 molar ratio (Chaudhary *et al*., 2008).

3.3. Biological activity of crude extracts and pure compounds

Plants of the genus *Drypetes* are used in the Subsaharan African and Asian traditional medicines due to its broad spectrum of biological and pharmacological activities. The varied ethnomedicinal uses of the different species of *Drypetes* have led to the initiation of many biological investigations. The table 2 presents the biological activities of crude extracts and some isolated coumpounds.

Table 2: Bioactivities and toxicity of crude extracts and isolated compounds from the genus *Drypetes*

Plant name	Part of plant	Isolated compound / crude extract	Reported bioactivity	Reference
D. chevalieri	stem	furanoeudesm-1-on-13-oic acid **100**	Antileishmanial	Wansi *et al*., 2007
D. congestiflora	stem	hoaensieremone **107**	Active against human lung adenocarcinoma cell line A 549 and murine mouse melanoma cell line B16 F10	Chen *et al*., 2015
D. gerrardii		crude extract	Antiplasmodial and antileishmanial	Hata *et al*., 2014
		resinone **66**	Antiplasmodia and not toxic against rat myoblast cell line L6	Ng'ang'a *et al*., 2011; 2012
		5*β*,24-cyclofriedelan-3-one **20**	Antiplasmodial and mild toxic against rat myoblast cell line L6	
	stem	drypetenone D **92**	Antiplasmodial, antileishmanial, antitrypanosomal, not toxic against rat myoblast cell line L6 and not active in *Plasmodium berghei* mouse model	Hata *et al*., 2014;
		drypetenone E **93**	Antiplasmodial, antileishmanial, antitrypanosomal and not toxic against rat myoblast cell line L6	
	leaves	crude extract	Antitrypanosomal	
		putranoside A **62**	Antileishmanial, antitrypanosomal, not active against *Plasmodium falciparum* NF54 and not toxic against rat myoblast cell line L6	
D. gossweileri	stem bark	crude extract	Antibacterial, antifungal and not toxic in animal experiment	Ndouga *et al*., 1991; Ijah and Ojebanji, 2003; Tan *et al*., 2006; Ngouana *et al*., 2010; 2011
		β-amyrone **43**, *N-β-D*-glucopyranosyl-*p*-hydroxyphenylacetamide **117**	Antifungal	Matochko, 2010; Ata *et al*., 2011
	cork	essential oil	Antifungal	Ndonkeu *et al*., 2013
	bark	stearic acid **140**	Active against human hepatoma cell lines HepG2 and Hep3B; low toxic against human normal cell line	Dupont *et al*., 1997; Tang *et al*., 2007
	not reported	maslinic acid **49**	Antidiabetic	Sow *et al*., 1994; Hou *et al*., 2009
	bark	*N-β-D*-glucopyranosyl-*p*-hydroxyphenylacetamide **117,** *β*-amyrone **43**	Antidiabetic	Matochko, 2010; Ata *et al*., 2011
	stem bark	crude extract	Analgesic in animal experiment	Bomba *et al*., 2013
	bark	*N-β-D*-glucopyranosyl-*p*-hydroxyphenylacetamide **117**	Acetylcholinesterase inhibition,	Matochko, 2010; Ata *et al*., 2011

		crude extract	Insecticidal against *Sitophilus zeamais* and *Rhyzopertha dominica*	Aba *et al*., 2013
D. hainanensis	stems + leaves	crude extract	Antioxidant	Chen *et al.*, 2011; 2014
	leaves	hainanenone **34**	Active against human hepatom cell line BEL7402, human lung adenocarcinoma	
		drypetesin A **112,** drypetesin B **113,** drypetesin C **114**	Active against human hepatoma cell line HepG2, human breast adenocarcinoma cell line MCF-7, and human lung carcinoma cell line A-549 cancer cell lines	Zhang *et al*., 2015
D. hoaensis	roots	(*E*)-caffeoyloxyfriedelan-7-one **39**, 3*α*-(*E*)-*p*-coumaroyloxyfriedelan-7-one **40**, 3 *β*-hydroxyfriedelan-12-one **27** hoaensifuranonal **105**, hoaensieremodione **106**, hoaensieremone **107**	Active against hepatocarcinoma cell line HepG2 active against acute lymphoblastic leukemia cell line MOLT-3 active against human cholangiocarcinoma cell line HuCCA-1 and hepatocarcinoma cell line HepG2	Wittalai *et al*., 2014
D. inaequalis	stem	lup-20(29)-en-3 *β*,6*a*-diol **67**	Antibacterial	Awanchiri *et al.*, 2009
	ripe fruit	28*β-D*-glucopyranosyl-30-methyl-3*β*-hydroxyolean-12-en-28,30-dioate **50**		
D. laciniata	whole stem	3*β*-hydroxyfriedelane-7,12,22-trione **16**, chikusetsusaponin IVa methyl ester **56**	Antibacterial	Fannang *et al*., 2011
D. littoralis	stem	crude extract	Antiviral and against Epstein Barr virus DNA polymerase	Chiou, unpublished study
		amentoflavone **127**	Antiplasmodial and toxic against rat myoblast cell line L6	Lin *et al*., 2001; Ng'ang'a *et al*., 2012
D. molunduana	stem bark	crude extract	Analgesic and antiinflammatory in animal experiment	Wandji *et al*., 2000; Nke *et al.*, 2001; 2003
		drypemolundein A **99**	Antiinflammatory and analgesic in animal experiments	
		oleanolic acid **48**	Antidiabetic	Hou *et al*., 2009
D. natalensis	bark, root	crude extract	Antitrypanosomal, antileishmanial, antiplasmodial and not toxic against rat myoblast cell line L6	Malebo *et al*., 2009
D. paxii	stems	12*β*-hydroxyfriedelane-3,15-dione **24**, 3*β*-hydroxyfriedelan-25-al **25**, friedelin **13,** friedelan-7-one **14** and 28*β-D*-glucopyranosyl-3*β*-	Antibacterial	Chiozem *et al*., 2009

		hydroxyolean-12-en-28-oate **52**		
D. perreticulata	twigs and leaves	crude extract	Antibacterial and broad spectrum cytotoxic activity	Chen *et al*., 2012
		dryperrein D **98**	Antibacterial, antifungal	Ge *et al.*, 2014
		crude extract dryperrein A-D **95-98**	Active against human lung tumor cell line A549 and leukemia cell line HL60	
D. roxburghii	seeds	putrin	Antibacterial, Dnase and Rnase inhibition and antifungal	Tomar *et al*., 2014
		crude extract	Not toxic against *Artemia salina*	Raghavendra *et al*., 2010
	stem bark		Highly toxic against *Artemia salina*	Krishnaraju *et al*., 2005
	fruits	nanoparticles of metallic silver	Antiplasmodial, not toxic against the fish *Poecilia reticulata*	Haldar *et al.*, 2013
	leaves	crude extract	Antibacterial and antifungal	Kumar *et al*., 2006
	leaf + fruit		Antifungal	Kuri *et al*., 2010, 2011
	leaf	essential oil	Antifungal	Tripathi and Kumar, 2007; 2013; 2014a; 2014b; Pandey and Tripathi, 2011
	bark	crude extract	Active against human hepatocellular carcinoma cell line HepG2 and low toxic against *Artemia salina*	El-Manawaty *et al.*, 2013
	trunc bark	putanjivadione **8**	Active against hepatocellular carcinoma cell line BEL7402, human lung cancer cell line A549 and leukemia cell line HL60	Garg and Mitra, 1968; Chen *et al.*, 2014
	leaves	crude extract	antidiabetic in animal experiment (EtOH extract); acute oral toxicity in animal experiment (70% MeOH extract); mitosis-disruptive chromosomal changes in bone marrow cells in animal experiment (80% EtOH extract)	Varma *et al.*, 2010; Rajahamsa *et al*., 2013; Awashthy *et al.*, 2000
	seeds		Central nerval system depressant activity in animal model; not toxic against *Artemia salina*	Sudharshan *et al.*, 2009; Raghavendra *et al*., 2010
	all parts		Antioxidant	Chinmaya *et al.*, 2009
	stems			Shahwar *et al*., 2012
	leaf + stem			Rajahamsa *et al.*, 2013
	leaves		Antiinflammatory in animal experiment (ether, acetone, MeOH); acute oral toxicity in animal experiment (70% MeOH extract)	Reanmongkol *et al*., 2009; Kaushik *et al.*, 2012; Rajahamsa *et al.*, 2013;
	leaves seeds	crude extract	Analgesic in animal experiment	Reanmongkol *et al.*, 2009
				Sudharshan *et al.*, 2009
	seeds	trypsin inhibitor	Inhibition of bovine trypsin in a 1:1 molar ratio	Chaudhary *et al*., 2008

		crude extract	Antiemetic in animal experiment	Mughal and Mahboob, 2013
	seed kernel	essential oil	Insecticidal against *Bruchus pisorum*	Kumar, 2014b
		volatile constituents of essential oil	Insecticidal against *Trogoderma granarium*	Tripathi and Kumar, 2007
D. sepiaria	leaves	crude extract	Active against cervical cancer cell line SiHa; antiinflammatory in animal experiment, antioxidant and anthelmintic against *Pheretima posthuma*	Gadamsetti *et al*., 2013a; 2013b
D. tessmanniana	stem bark	3*β*-*O*-(*E*)-3,5-dihydroxycinnamoyl-11-oxo-olean-12-ene **61** and 3*β*,6*α*-dihydroxylup-20(29)-en **69**	Antibacterial, not active against *Candida albicans* LMP709U and *Microsporum audouinii* LMP725D	Dongfack *et al*., 2008; Kuete *et al*., 2010

3.3.1. Antileishmanial and antitrypanosomal activity

No species of the genus *Drypetes* is traditionally used to treat leishmaniasis, African sleeping sickness and Chagas disease (trypanosomiasis). However, some crude extracts and compounds have been tested on these diseases. The DCM-MeOH (1:1) stem extract of *D. gerrardii* showed moderate *in vitro* activity against *Leishmania donovani* MHOM/ET/67/L82 with IC_{50} 7.31 mg/mL. The isolated saponin putranoside A **62** and phenanthrenone derivative, drypetenone D 92, showed weak activity against *Leishmania donovani* with IC_{50} 7.8 µM and 14.0 µM, respectively compared to the positif control (miltefosine IC_{50} of 0.552 µM). The same solvent extract of the leaves showed moderate activity against *Trypanosoma brucei rhodesiense* STIB 900 strain, with IC_{50} 12.1 mg/mL, while the same isolated compounds showed weak activity against *Trypanosoma brucei rhodesiense* with IC_{50} 18.0 µM and 6.0 µM, respectively compared to the positif control (melarsoprol IC_{50} of 0.003 µM) (Hata *et al*., 2014). Malebo *et al.* (2009) reported the antileishmanial and antitrypanosomal activities of the ethanolic stem and the root bark extracts of *D. natalensis* against *Trypanosoma brucei rhodesiense* STIB 900 with IC_{50} 10.70 µg/mL and against *Leishmania donovani* MHOM-ET-67/82 with IC_{50} 19.0 µg/mL for the stem bark, and with IC_{50} 12.10 µg/mL against *Trypanosoma brucei rhodesiense* STIB 900, and IC_{50} 29.7 µg/mL against *Leishmania donovani* for the root bark. The DCM-MeOH (1:1) extract of the stem of *D. chevalieri* delivered the furanoeudesm-1-on-13-oic acid **100** which displayed significant antileishmanial activity against *Leishmania major* (88/DESTO) promasitigotes with IC_{50} 40.0 µg/mL compared to the positive control pentamidine with IC_{50} 38.0 µg/mL (Wansi *et al.*, 2007). Improved "crude" drugs from active fractions of *D. natalensis* and *D. chevalieri* might be alternatives to modern antileishmanial and antitrypasnosomal drugs, subject to careful toxicity studies employing human normal cell lines and toxicity tests in animal model.

3.3.2. Antiplasmodial activity

Five species of *Drypetes* (*D. aubrévillei, D. gerrardii, D. natalensis, D. gossweileri* and *D. roxburghii*) have been traditionally used in herbal medicine to treat malaria and fever, and as insect-repellent. Only three species and the isolated compounds have been assessed for their antimalarial activity (Hata *et al.*, 2014; Ng'ang'a *et al.*, 2011; 2012; Lin *et al.*, 2001; Haldar *et al.*, 2013).

The DCM-MeOH (1:1) stem extract of *D. gerrardii* inhibited the chloroquine-resistant African *Plasmodium falciparum* NF54 with IC_{50} 0.50 µg/mL. From this extract, the isolated compounds, drypetenone D **92** and drypetenone E **93**, showing weak activity against *Plasmodium falciparum* NF54 with IC_{50} 0.9 µM and 2.04 µM, respectively compared to the positive control chloroquine with IC_{50} 0.004 µM. These compounds also showed a CC_{50} 68.4 µM and CC_{50} 64.0 µM, respectively against rat myoblast cell line L6, compared to the positive control podophyllotoxin with CC_{50} 0.019 µM, resulting in a selectivity index SI 71 and 31.4, respectively. However, drypetenone D **92** was inactive *in vivo* against *Plasmodium berghei* mouse model (Hata *et al.*, 2014). In addition, 5*β*,24-cyclofriedelan-3-one **20** isolated from the EtOAc extract of the stem of *D. gerrardii*, exhibed antiplasmodial activity with IC_{50} 2.2 µg/mL compared to the positive control chloroquine with IC_{50} 0.063 and artemisinin with IC_{50} 0.002. This compound displayed and CC_{50} 21.2 µM against rat myoblast cell line L6 compared to podophyllotoxin with a CC_{50} 0.009 µM, resulting in a selectivity index SI 9.64. Resinone **66** isolated from the same extract, displayed high antiplasmodial activity with IC_{50} 0.09 µg/mL and displayed and CC_{50} of 84.8 µM against rat myoblast cell line L6, resulting in a favourable selectivity index of 942.2 (Ng'ang'a *et al.*, 2011; 2012). Lin *et al.*, (2001) reported the potent antiplasmodial activity of amentoflavone **128** with IC_{50} 2.6 µg/mL, compared to the positive control chloroquine with IC_{50} 0.063 µg/mL and artemisinin with IC_{50} 0.002 µg/mL, but Ng'ang'a *et al.* (2011; 2012) indicated that the activity observed was probably due to the toxicity rather than selective activity against the parasite. The EtOH extract of the root bark of *D. natalensis* displayed IC_{50} 1.06 µg/mL against the chloroquine-resistant *Plasmodium falciparum* K1 (Thailand) compared to chloroquine with IC_{50} 0.063 µg/mL and artemisinin with IC_{50} 0.002 µg/mL, and a CC_{50} 19.0 against rat skeletal myoblast cell line L-6. Activities resulted in an SI value of 17.9, indicating no toxicity when applied in antiplasmodial therapy. Furthermore, the EtOH extract of the stem bark displayed an IC_{50} 1.42 µg/mL against *Plasmodium falciparum* K1 compared to chloroquine with IC_{50} 0.063 µg/mL and artemisinin with IC_{50} 0.002 µg/mL, and a CC_{50} 88.9 against rat skeletal myoblast cell line L-6. Activities resulted in an SI 62.61 (Malebo, 2009), indicating as well no toxicity when applied in antiplasmodial therapy. Interestingly, highly stable silver nanoparticles with average dimension of 26.6 nm synthesized by dried green fruit of *D. roxburghii* displayed strong mosquito larvicidal activity against *Culex quinquefasciatus* and *Anopheles stephensi*. The 50 % lethal concentration (LC_{50}) values for second, third and fourth larval instars after 24 h of exposure to the nanoparticles were 0.8632, 1.1619, and 1.2814 ppm against *Culex quinquefasciatus*, and 0.7329, 0.8397 and 0.9848

ppm against *Anopheles stephensi*, respectively. Toxicity tests on the non-target organism *Poecilia reticulata* (Pisces) showed no harmful effect at 0.8397 ppm, the LC_{50} concentration used for third instar *A. stephensi* larvae (Haldar *et al.*, 2013). The extracts and isolated compounds showed some significant antiplasmodial activity associated with a high cytotoxicity against rat skeletal myoblast cell line L-6. These result showed that the extract and the compounds can no kill the parasites without damaging mammalian cells. However, further research work on *D. natalensis* is urgently needed

3.3.3. Antibacterial activity

All species of the genus *Drypetes* are locally used as antimicrobial agents. Due to the prevalence of multi-drug resistant bacteria and their low susceptibility to antibiotics, nearly all extract have been tested for their antibacterial activity. The DCM extract of the stem bark of *D. gossweileri* showed antibacterial activity with MIC values of 0.25 to 1.00 mg/mL against *Staphylococcus aureus*, *Streptococcus faecalis*, *Shigella dysenteriae*, *Yersinia enterocoleteca*, *Enterobacter cloacae* and *Salmonella* sp. (Ndouga *et al.*, 1991). The aqueous and ethanolic extracts of the stem bark clearly inhibited *S. aureus*, *Pseudomonas aerugosina*, *Klebsiella* sp., *Proteus* sp. and *Escherichia coli*, causative agents of urinary tract infections, with the ethanol extract exhibiting the highest inhibitory activity with MICs ranging between 3% and 7% (Ijah and Oyebanji, 2003). Furthermore, the DCM-MeOH (1:1) extract of the bark displayed antibacterial activity against *Helicobacter pylori* strain CCUG 39500 with MIC 0.78 mg/mL compared to amoxicillin with 0.0062 mg/mL and against *Campylobacter jejuni/coli* strain CPC-022004 as well with 0.78 mg/mL, compared to amoxicillin with MIC 0.0062 mg/mL (Tan *et al.*, 2006). Importantly, Ngouana *et al.*, (2010) reported that the extract did not show any signs of toxicity in rats up to 1000 mg/kg dose, with the exception of male rats at 1000 mg/kg dose where a light diminution in body weight was observed. Morphological examination of various organs and statistical analysis of relatives organs weight revealed that there were no differences between the control groups which received distilled water and maize oil and treated rats. Furthermore, lup-20(29)-en-3β,6α-diol **67** and 28β-*D*-glucopyranosyl-30-methyl-3β-hydroxyolean-12-en-28,30-dioate **50** isolated from the whole stem of ripe fruit of *D. inaequalis*, assayed by agar diffusion well at a concentrations of 200 µg/mL, displaying inhibition zone diameters of 11 to 15 mm against *S. aureus*, *E. coli*, and *Salmonella typhi*, compared to the positive control gentamycin displaying 34, 35 and 42 mm of inhibition zone (Awanchiri *et al.*, 2009). In addition, from the methanol extract of the whole stem of *D. laciniata*, the isolated compound, 3β-hydroxyfriedelane-7,12,22-trione **16** showed antimicrobial activity against *S. aureus* ATCC25922, *S. typhi* ATCC6539, *Pseudomonas aeruginosa* ATCC27853, *E. coli* ATCC 10536, with gentamicin as positive control angainst *E. coli* with MIC 256 mg/mL, *P. aeruginosa* with MIC 256 mg/mL, and *S. typhi* with MIC 512 mg/mL. Chikusetsusaponin IVa methyl ester **56** displaying also inhibitory activities on the growth of *E. coli* with MIC 256 mg/mL and *S. typhi* with MIC 512 µg/mL (Fannang

et al., 2011). From the methanolic stem extract of *D. paxii*, 12α-hydroxyfriedelane-3,15-dione **24** and 3β-hydroxyfriedelan-25-al **25** together with friedelin **13**, friedelan-7-one **14**, and 28β-*D*-glucopyranosyl-3β-hydroxyolean-12-en-28-oate **52** were tested in an agar well diffusion assay at 200 µg/mL displaying inhibition zones of 17, 14, 11, 10, 15 respectively 21 mm against *S. aureus*, compared to gentamycine with 34 mm, while compound **52** was as well active in this assay against *E. coli* with 18 mm and *S. typhi* with 17 mm, compared to gentamycine displaying 35 respectively 42 mm of inhibition zone diameter (Chiozem *et al.*, 2009). Furthermore, the extracts of *D. perreticulata* were reported to display marginal antibacterial actvity against *S. aureus* ATCC 1339, *B. subtilis* ATCC 6633, *P. aeruginosa* ATCC 14886 and *E. coli* ATCC 8739 (Chen *et al.*, 2012). The twigs and leaves of this plant extracted with EtOH/H_2O (95:5) afforded dryperrein D **98** which displaying marginal activity against *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *Micrococcus luteus* ATCC 9341 and *B. subtilis* in a microdilution assay compared to the positive control ofloxacin (Ge *et al.*, 2014). 3β-*O*-(*E*)-3,5-dihydroxycinnamoyl-11-oxo-olean-12-ene **61** and 3β, 6α-dihydroxylup-20(29)-ene **69** were submitted to paper disc agar diffusion assays employing methicillin-resistant *S. aureus*, *S. faecalis* LMP806, *B. cereus* LMP716, β-lactamase positive *E. coli* LMP701, ampicillin-resistant *Klebsiella pneumoniae* LMP803, ampicillin-resistant *Shigella dysenteriae* LMP820, carbenicillin-resistant *Pseudomonas aeruginosa* LMP804, and chloramphenicol-resistant *Citrobacter freundii* LMP802. MICs determined at 80 µg per disc. displayed low activities in a range of > 625 to 156.25 µg/mL compared to gentamycin with 4.88 to 39.06 µg/mL (Kuete *et al*., 2010). The DCM-MeOH (1:1) extract of the the leaves of *D. roxburghii* was reported to show antibacterial activity in a preliminary assay using agar dilution-streak method, where extracts were mixed with agar at 500 µg/mL and 1000 µg/mL and test strains streaked at the solidified surface. At 500 µg/mL, the extract completely inhibited the growth of *Micrococcus luteus* ATCC 9341, *Streptococcus faecalis* MTCC 8043 and *Staphylococcus epidermidis* ATCC 12228 (Kumar *et al.*, 2006). In addition, from seeds extract of the plant, a multifunctional ~12 kDa heterodimeric protein named putrin was isolated and shown to inhibit weakly *Micrococcus flavus* and *Bacillus subtilis.* Values of antibacterial activity were not shown (Tomar *et al.*, 2014). Interestingly, it was noted that the methanolic seeds extract was not toxic in *Artemia salina* assay displaying LD_{50} 427.74 µg/mL (Raghavendra *et al.*, 2010). A more promising ethnopharmacological approach would be to focus on plants used for the treatment of wounds to prevent infections (main causative agent: *Staphylococcus aureus*), urinary tract infections (*Escherichia coli*), ear infections (*Streptococcus pneumoniae*), or gonorrhoea (*Neisseria gonorrhoea*) using multiresistant test strains.

However, the systematic data on the chemical constituents and their pharmacological activities are limited. Thus, studies on the antimicrobial effects and mechanisms of the genus *Drypetes* are long overdue.

3.3.4. Antifungal activity

The antifungal properties of the DCM-MeOH (1:1) stem bark crude extract of *D. gossweileri* were assayed by broth dilution method against *Candida albicans*, *C. glabrata*, *Microsporum langeroinii*, *M. gypseum*, *Trichophyton rubrum*, *T. mentagerophytes* and *Aspergillus flavus* resulting in MICs 24.41, 48.84, 12500, 12500, 12500, 6250 and 12500 µg/mL, compared to the positive control amphothericin with MIC 2.44 µg/mL for *Candida*, *Microsporum* species and with MIC 3.125 µg/mL for *Trichophyton* and *Aspergillus*. Moreover, the extract was tested for acute toxicity on male and female albino Wistar rats. Extract doses of 0, 4, 8, and 12 g/kg body weight were administered *per os* to 4 groups of animals of both sex. The rats were observed for 48 h for death and for 7 days for toxic effects. Interestingly, no toxic effects were recorded up to a dose of 12 g/kg of body weight (Ngouana, 2011). From the MeOH extract of the stem bark, the isolated *β*-amyrone **43** and *N*-*β*-glucopyranosyl-*p*-hydroxyphenylacetamide **117**, exhibiting activity against *C. albicans* with MIC 16 µg/mL and 8.0 µg/mL, respectively (Ata *et al.,* 2011). The aglycone of compound **117** showed weak active in this bioassay, with an MIC 32 µg/mL, indicating that this activity migth be due to the presence of a *N*-glucose moiety in compound **117** (Matochko, 2010; Ata *et al*., 2011). At 50 ppm, the essential oil of the cork of *D. gossweileri* inhibited mycelial growth of *Colletotrichum dematium* and *Acremonium apii* by 100% (Ndonkeu *et al*., 2013). Dryperrein D **98** isolated from the twigs and leaves of the EtOH/H_2O (95:5) extract of *D. perreticulata* displayed antifungal activity against *C. albicans* ATCC 1600 and *Saccharomyces sake* ATCC 26421strains at 50 µg/mL in agar dilution method with amphothericin B as positive control (Ge *et al.*, 2014). Furthermore, the DCM -MeOH (1:1) extract of the the leaves of *D. roxburghii* was reported to show antifungal activity in a preliminary assay using agar dilution-streak method, where extracts were mixed with agar at 500 µg/mL and 1000 µg/mL and test strains streaked at the solidified surface. At 500 µg/mL, the extract completely inhibited the growth of *C. albicans* MTCC 10231, but not of *A. niger* MTCC 1344, compared to the positive control amphotericin B which showed complete inhibition at 3 µg/mL (Kumar *et al.*, 2006). In addition, aqueous leaves and fruit extracts of the same plant showed a reduction to 9.33% of *Solanum melongena* seed infection by *A. flavus*, *Fusarium oxysporum*, *Curvularia lunata*, and *Phomopsis vexans* compared to 66% fungal infection of untreated seeds (Kuri *et al*., 2010, 2011). The essential oil of the same plant was found to be fungicidal and thermostable at its MIs of 400 ppm against *A. flavus* and *A. niger.* The oil protected peanut seeds completely for 6 months at 0.25 and 0.38 mL in containers of 250 mL capacity holding 200 g seeds against above fungi and the insect pest *Trogoderma granarium*. It did not exhibit any adverse effect on seed germination, seedling growth

and general health and morphology of plants (Tripathi and Kumar, 2007). The leaves oil of this plant inhibited mycelial growth of *Aspergillus flavus*, *A. niger*, *A. ochraceus*, and *A. terreus* with 48.48, 38.75, 15.71, 48.23% at a concentration of 500 ppm and of *Fusarium oxysporum*, *F. solani*, *F. chlamydosporum*, *F. equestri*, *F. monoliforme*, *F. avenaceum*, *Alternaria solani* and *Humicola griseus* at 700 ppm, the growth of *Absidia spinosa*, *Acremonium album*, *F. nivale* and *Penicillium funiculosum* (95%), and at 1000 ppm the growth of *Rhinopsus nigricans*, *P. chrysogenum*, *P. glabrum* and *P. oxalicum*. Moreover, the fungitoxicity was not destroyed by autoclaving and storage upto 120 days (Pandey and Tripati, 2011; Kumar, 2013, 2014a, 2014b). Interestingly, a multifunctional ~12 kDa heterodimeric protein named putrin reported from the seeds displayed an IC_{50} value of 34.7 µM against *A. flavus* (Tomar *et al.*, 2014). Compounds, 3*β*-*O*-(*E*)-3,5-dihydroxycinnamoyl-11-oxo-olean-12-ene **61** and 3*β*, 6*α*-dihydroxylup-20(29)-ene **69** isolated from the methanolic extract of the stem bark of *D. tessmanniana*, were inactive to paper disc agar diffusion assays employing the fungi *Candida albicans* LMP709U and *Microsporum audouinii* LMP725D (Kuete *et al.*, 2010).

3.3.5. Cytotoxic activity

Hoaensieremone **107** isolated from the air-dried 95% EtOH/H_2O extract of the stems of *D. congestiflora* was shown to exhibit moderate cytotoxic activity against human lung adenocarcinoma cell line A 549 as well as murine mouse melanoma cell line B16 F10, with IC_{50} values of 27.5 respectively 41.3 µM (Chen *et al.*, 2015). Stearic acid **140** reported from the bark of *D. gossweileri* (Dupont *et al.*, 1997) was reisolated from *Oldenlandia diffusa* and proven to display significant inhibitory effects on the growth of human hepatoma cell lines HepG2 and Hep3B with IC_{50} 90 µM respectively 130 µM, and displayed only 20% inhibition of the normal human liver cell line WRL-68. Mechanistic studies showed that both cell types were more sensitive towards stearic acid when comparing with other fatty acids, and potential for hepatoma treatment was suggested (Tang *et al.*, 2007). Hainanenone **34** isolated from the EtOH extract of the leaves of of *D. hainanensis*, displayed moderate growth inhibitory activity against human hepatom cell line BEL7402, human lung adenocarcinoma cell line A549, and human leukemia cell line HL60 at the concentration of 10^{-5} mol/L with 3.0, 9.7 respectively 4.1% inhibition compared to adriamycin displaying 54.4, 72.2 respectively 89.6% inhibition (Chen *et al.*, 2014). Further phytochemical investigation of *D. hainanensis* resulted in the isolation of three phenylpropanoids, named drypetesins A-C **112-114** exhibiting potent cytotoxic activities against human hepatoma cell line HepG2, human breast adenocarcinoma cell line MCF-7, and human lung carcinoma cell line A-549 cancer cell lines with IC_{50} values of 5.6, 8,2 and 6.7 µM for drypetensin A **112**, 12.2, 9.4 and 12.5 µM for drypetensin B **113** and 14.8, 12.4 and 10.8 µM for drypetensin C **112** compared to doxorubicin displaying 1.3, 0.78 and 0.57 µM (Zhang *et al.*, 2015). From the DCM extract of the roots of *D. hoanensis*, (*E*)-caffeoyloxyfriedelan-7-one **39**, 3*α*-

(*E*)-*p*-coumaroyloxyfriedelan-7-one **40**, and 3α-hydroxyfriedelan-12-one **27** were isolated and evaluated against acute lymphoblastic leukemia cell line MOLT-3, human cholangiocarcinoma cell line HuCCA-1, human lung cancer cell line A549 and hepatocarcinoma cell line HepG2 displaying highly significant cytotoxicity against the latter cell line with IC_{50} values of 0.1, 3.1, 0.3 µM, respectively. Furthermore, five compounds namely hoaensibenzofuranal **103**, hoaensieudesone **104**, hoaensifuranonal **105**, hoaensieremodione **106** and hoaensieremone **107** were submitted to cytotoxicity assays. Compounds **105** and **107** showed moderate cytotoxic activity against acute lymphoblastic leukemia cell line MOLT-3 with IC_{50} values of 16.8 and 14.6 µM, while compound **106** showed weak cytotoxic activity with 74.8 µM. Compound **107** was weakly active against human cholangiocarcinoma cell line HuCCA-1 and hepatocarcinoma cell line HepG2 with IC_{50} of 51.9 and 72.4 µM (Wittalajai *et al.*, 2014). In addition, the petroleum ether extract of *D. perreticulata* exhibited a broad spectum cytotoxic activity with IC_{50} from 76.0 to 682.5 µg/mL in MTT assay (Chen *et al.*, 2012). *In vitro* cytotoxic activities against human lung tumor cell line A549 and leukemia cell line HL60 showed for dryperrein A **95** and B **96** only weak cytotoxicity against human lung cancer cell line A549 cell line with IC_{50} 91.72 µM and 88.54 µM, respectively, and against leukemia cell line HL60 with IC_{50} 68.59 µM and 65.08 µM, respectively. However, compounds dryperrein C **97** and D **98** displayed moderate inhibitory activities against A549 cell line, with IC_{50} of 8.50 and 9.45 µM, respectively. Interestingly, compounds **97** and **98** showed strong inhibition against the leukemia cell line HL60 with IC_{50} 1.95 and 1.37 µM, respectively. The cytotoxicity results suggested that the presence of Δ^1 double bond in dryperrein C **97** and D **98** is crucial to the cytotoxic activities of this class of dinorditerpenoids, while alteration of 6-substuent (OH/OMe) has little effect on their activities. Adriamycin was used as positive control with IC_{50} values of 0.47 µM and 0.12 µM against human lung cancer cell line A549 and leukemia cell line HL60, respectively (Ge *et al.*, 2014). A toxicity profile of these both compounds against humal normal cell lines still needs to be done before their medicinal potential can be commented. At 100 ppm, the methanolic bark extract of *D. roxburghii* displayed 93.47 % inhibition of human hepatocellular carcinoma cell line HepG2 compared to the positive control adriamycin with 100 %, while *Artemia salina* used in toxicity assay displayed only 10% inhibition at this concentration, compared to the leave extract of *Annona cherimolia* as positive control showing 100% inhibition. The negative control DMSO gave 0.6 respectively 3.3% inhibition, which was tolerable (El-Manawaty *et al.*, 2013). At 10^{-5} mol/L, putanjivadione **8** isolated from the trunk bark of *D. roxburghii* (Garg and Mitra, 1968) showed 4.0, 21.1 and 43.1% inhibition of hepatocellular carcinoma cell line BEL7402, human lung cancer cell line A549 and leukemia cell line HL60 compared to the positive control adriamycin displaying 54.5, 72.2 and 89.6 % inhibition, friedelin **13** was inactive in above cytotoxicity assays. Putranjivadione **8** is a keto derivative, and it was observed that the ketone groups at C-3 and C-7 considerably increased the cytotoxicity against

tumor cell lines compared to hainanenone **34** and friedelin **13** (Chen *et al.*, 2014). The methanolic extract from leaves of *D. sepiaria* exhibited cytotoxicity against cervical cancer cell line SiHa with an IC_{50} of 10 µg/mL (Gadamsetti *et al*., 2013a). Positive and negative controls are not reported.

3.3.6. Antidiabetic activity

No species of the genus *Drypetes* is traditionally used to treat diabetes. However, some crude extracts and compounds have been tested for antidiabetic activity. Maslinic acid **49** and oleonolic acid **48** delivering α-glucosidase inhibition with an IC_{50} value of 5.52 respectively 6.29 µg/mL (Hou *et al*., 2009). Compound, *N*-β-glucopyranosyl-*p*-hydroxyphenyl acetamide **117**, isolated from the methanolic extract of the bark of *D. gossweileri*, exhibiting high α-glucosidase inhibitory activity with IC_{50} 12.0 µM. Acidic hydrolysis afforded its aglycone, which exhibited an α-glucosidase inhibition activity with an IC_{50} 60.0 µM suggesting that the higher potency of compound **117** was due to the presence of an *N*-glucose moiety (Matochko, 2010; Ata *et al.*, 2011). In addition, β-amyrone **43** exhibited α-glucosidase inhibition with an IC_{50} value of 12 µM (Ata et al., 2011). For compounds **43** and **117**, no positive controls and toxicity against normal mammalian cell lines were reported. Furthermore, the ethanolic extract of the leaves of *D. roxburghii* was subjected to antidiabetic activity in rats where alloxan monohydrate (120 mg/kg b.w., i.p.) was used as the diabetogenic agent. At a dose of 250 mg/kg, significant antihyperglycemic activity on the 4th, 7th and 10th day post treatment with fasting blood glucose level of 258.23, 255.85, respectively 252.06 mg/dL compared to the positive control glibenclamide at a dose of 10 mg/kg displaying 205.25, 183.18, respectively 178.13 mg/dL was measured (Varma *et al.*, 2010). However, it should be pointed out that the 70 % methanol extract of dried leaves of the same plant showed acute oral toxicity with LD_{50} 500 mg/kg body weight in female Wistar albino rats (Rajahamsa *et al*., 2013), while the 80% EtOH (v/v) leaves extract significantly induced mitosis-disruptive chromosomal changes in bone marrow cells of mice when administered at 0.5, 1.0 or 2.0 g/kg body weight/day for seven consecutive days (Awasthy *et al*., 2000). Further work on the *D. gossweileri* and the respective compounds regarding toxicity is recommended, since they might be a good alternative in Subsaharan countries for the treatment of diabetes.

3.3.7. CNS depressant activity

Sudharshan *et al.* (2009) reported the CNS depressant activity of 100 mg/kg MeOH extract of *D. roxburghii* administered intraperitoneally (i.p.) seedsin a mouse model. Depression of the CNS was assessed with a digital actophotometer which operates on photoelectric cells connected with a counter, and records when a beam of light falling on the device's photocell is cut off by a test animal.

Locomotion was significantly inhibited (38.59%) 45 mins after dosing compared to 5 mg/kg i.p. diazepam (16.35%).

3.3.8. Analgesic activity

A recent investigation of the analgesic properties of an aqueous extract of *D. gossweileri* stem bark in mice and rats (Bomba *et al.*, 2013) revealed that both 100 and 200 mg/kg doses significantly decreased nociception induced by intraperitoneally (i.p.) administered acetic acid measured as writhing (abdominal constrictions and hind limbs stretching) inhibition percentage of 45.79 and 66.06% ($p < 0.01$ and $p < 0.001$), respectively. Similarly, analgesia for neurogenic and inflammatory pain were examined in rats by injecting 20 μL of 2.5% formalin into the subplantar of the right hindpaw, 1 h after the aqueous *D. gossweileri* extract had been administered. Sensation of pain was quantified from time spent licking the injected paw 0-5 min post-injection (first phase neurogenic pain indicator) and 15-30 min post-injection (second phase inflammatory pain indicator). In the first phase, 200 mg/kg aqueous extract significantly reduced (47.41% inhibition) pain sensation ($p < 0.01$). During the second phase, the effects of the aqueous extract on pain sensation were dose dependent: inhibition of 36.27% for 100 mg/kg, 55.84% for 200 mg/kg, and 65.4% for 400 mg/kg aqueous extract. Assessment of pain induced by pressure indicated that 100, 200 and 400 mg/kg doses of the aqueous extract significantly reduced pain sensation, with maximum inhibition (54.44%) observed with 200 mg/kg. The authors concluded that these results suggest the presence of secondary metabolites with analgesic properties in the aqueous extract of *D. gossweileri* (Bomba *et al.*, 2013). Pharmacological screening showed significant analgesic effects of a crude stem bark extract of *D. molunduana* and the isolated compound, drypemolundein A **99** (Nkeh *et al.*, 2001, 2003). An ether extract of *D. roxburghii* leaves administered orally at 100, 200, and 400 mg/kg resulted in dose dependent analgesic effects, against to counteract writhing pain following acetic acid treatment in mice (Reanmongkol *et al.*, 2009). The analgesic activity of the MeOH extract of *D. roxburghii* seeds was evaluated by tail flick method and activity was greater than the standard drug (Sudharshan *et al.*, 2009). Another *D. roxburghii* extract showed dose dependent analgesia again in an acetic acid-induced writhing model, but dose independent activity in hot plate and tail flick models, compared to indomethacin (a non-steroidal anti-inflammatory drug, NSAID) (Rajahamsa *et al.*, 2013).

3.3.9. Anti-inflammatory activity

Drypetes species have been traditionally used in herbal medicine to treat inflammation including edema and rheumatism; however, only three species have been assayed for their anti-inflammatory effects. The pharmacological screening of the stem bark crude extract of *D. molunduana* showed significant anti-inflammatory effects (Nkeh *et al.*, 2001). Drypemolundein A **99** isolated from this extract, significantly reduced paw edema with 57.57 % and 66.66 % inhibition at 1 h intervals, respectively at doses of 10 and 20 mg/kg *per os*. The ether extract of *D. roxburghii* leaves showed

moderate anti-inflammatory activity at (100, 200, and 400 mg/kg, administered orally) in carrageenin-induced paw edema, decreased croton oil-induced anus edema at 800 mg/kg high dose in rats and displayed a dose-dependent (1.25, 2.5, and 5.0 mg/ear) inhibitiion of croton oil-induced ear edema in mice (Reanmongkol *et al.*, 2009). Kaushik *et al.* (2012) reported that the acetone extract of the leaves showed significant reduction (32.47% and 24%, respectively) in a rat model of carregeenan or dextran-induced inflammation. When orally administered at 500 mg/kg, the 70% MeOH extract of *D. roxburghii* dried leaves and stems showed anti-inflammatory activity by significantly suppressing carrageen-induced paw oedema, to comparable indomethacin (15 mg/kg) treatment levels. Croton-induced ear edema was also significantly reduced (49.2%) when the MeOH extract was applied topically (5.0 mg/ear), again to indomethacin comparable levels treatment (59.1%) (Rajahamsa *et al.*, 2013), while the 80% EtOH (v/v) leaf extract significantly induced mitosis-disruptive chromosomal changes in bone marrow cells of mice when administered at 0.5, 1.0 or 2.0 g/kg body weight/day for seven consecutive days (Awasthy *et al*., 2000). The petroleum ether, EtOAc, MeOH and aqueous extracts obtained from leaves of *D. sepiaria* were tested for anti-inflammatory activity with variable results. The MeOH extract inhibited inflammation *in vitro* to 85-90% as measured by HRBC stabilization method; *in vivo* assessment as measured by the paw edema method revealed 40-45% inhibition of inflammation after/upto/at 6 hrs, compared to 50.04% for the standard (Gadamsetti *et al.*, 2013a). Further work on the *D. molunduana, D. sepiaria* and the respective compounds regarding toxicity is recommended. This study requires the positive controls for comparative efficacy.

3.3.10. Antioxidant activity

The combined ethanol (EtOH) extracts of stem and leaves and additional extracts from petroleum ether, EtOAc, butanol and water of *D. hainanensis* displayed an IC_{50} of 77.3, 115.2, 51.4, 342.9, and 205.7 μg/mL as measured by diphenylpicrylhydrazyl (DPPH) and 11,712.2, 10,820.9, 14,386.4, 1,157.6, and 5,584.1 μmol Fe^{2+}/g as measured by ferric reducing antioxidant power (FRAP) method. Results indicate moderate antioxidant activity when compared to ascorbic acid and BHT showing an IC_{50} of 10.7 μg/mL, 47.1 μg/mL for DPPH and 18,022.8 14 568.7 μmol $Fe^{2+/}$g for FRAP method (Chen et al., 2011). As well, the petroleum ether, DCM, EtOAc and MeOH extracts of *D. perreticulata* possess moderate antioxidant activity (Chen *et al.*, 2012). The petroleum ether, EtOAc, MeOH and aqueous extracts obtained from *D. sepiaria* leaves were assessed with an *in vitro* antioxidant method. The MeOH and EtOAc extracts provided the most potent and concentration dependent DPPH radical scavenging activity with IC_{50} values of 95.43 μg/mL and 94.1 μg/mL respectively, compared to the ascorbic acid standard of 3.6 μg/mL; the same extracts also had the most potent and concentration dependent 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical cation decolourisation activity with IC_{50} values of 67.05 μg/mL and 55.25 μg/mL respectively, compared to the standard gallic acid with IC_{50} of 8.7 μg/mL (Gadamsetti et al., 2013a). Chinmaya *et al.* (2009)

reported the antioxidant activity of a MeOH extract of *D. roxburghii* measured by the DPPH method at 0.5 and 1.0 mg/mL concentrations exhibited high free radical scavenging activity in a dose dependent manner with 73 and 88.19% respectively, compared to ascorbic acid (95.04 and 97.30% respectively). Antiradical activity of the ethyl acetate extract of *D. roxburghii* stems was confirmed by a decrease in absorbance at 517 nm using the DPPH method. The extract exhibited high activity (91.9% inhibition with IC_{50} 4 µg) compared to gallic acid (94.3% inhibition with IC_{50} 2 µg), ascorbic acid (92.6% inhibition with IC_{50} 3 µg), and quercetin (87.3% inhibition with IC_{50} 5 µg). The extract showed high antioxidant activity when measured by the FRAP method with 638.7 equivalent to $FeSO_4.7H_2O$ (µM), and displayed a higher absorbance of 1.393 at 695 nm for antioxidant capacity (TAC), compared to gallic acid with an absorbance of 1.213 (Shahwar *et al.,* 2012). The combined extracts of dried *D. roxburghii* leaves and stems displayed significant DPPH and H_2O_2 free radical scavenging activity in a dose dependant manner, and was only marginally lower when compared to the ascorbic acid standard (Rajahamsa *et al.,* 2013).

3.3.11. Antiviral activity

In a preliminary study the MeOH extract of *D. littoralis* was found to possess activity against Epstein-Barr virus DNA polymerase (Lin *et al.,* 2001).

3.3.12. DNAse and RNAse inhibition *in vitro*

A multifunctional ~12 kDa heterodimeric protein named putrin isolated from the seeds of *D. roxburghii* was purified, characterised and cloned. Putrin inhibited the protein synthesis with an IC_{50} of 6.6 µM and demonstrated a much lower cell-free translational inhibitory activity as compared with other 2S proteins and small RIPs (Tomar *et al.,* 2014).

3.3.13. Bovin trypsin inhibition *in vitro*

A highly stable trypsin inhibitor was isolated from the seeds of *D. roxburghii*. The protein consists of a single polypeptide chain of 34 kDa and inhibits bovine trypsin in a 1:1 molar ratio (Chaudhary *et al.,* 2008)

3.3.14. Acetylcholinesterase inhibition *in vitro*

N-β-glucopyranosyl-*p*-hydroxyphenylacetamide **117**, showed moderate activity against acetylcholinesterase with IC_{50} 78.1 µM compared to galanthamine with 0.9 µM (Matochko, 2010; Ata *et al*., 2011).

3.3.15. Antiemetic.activity *in vivo*

An aqueous extracts of *D. roxburghii* administered at 25, 50, 75, and 100 mg/kg, displayed a significant, dose-deprendent retching reduction in copper sulfate ($CuSO_4$)-induced emesis in four days old chicks (61.7, 67.6, 70.8, and 78.9%, respectively) (Mughal and Mahboob, 2013).

3.3.16. Insecticidal activity *in vitro*

The ethyl acetate (EtOAc) and DCM extracts of the bark of *D. gossweileri* were found to be effective against the maize weevil *Sitophilus zeamais* and the grain borer *Rhyzopertha dominica* at 1.0, 0.5, 0.250 g/10 mL (Aba *et al.*, 2013). The seed kernel oil of *D. roxburghii* showed 100% repellency against the Indian seed storage insect *Bruchus pisorum* (Linn.), which was present in all 25 collected storage seed samples of *Dalbergia sissoo* Roxb, at a concentration of 0.02 mL (Kumar, 2014b). Volatile constituents extracted in the form of essential oil from *D. roxburghii* were found to protect againsts the insect *Trogoderma granarium* isolated from stored peanut seeds. This oil protected the peanut seeds completely for six months at 0.25 and 0.38 mL in 250 mL containers holding 200 g of seeds, and did not exhibit any adverse effects on seed germination, seedling growth as well as the general health and morphology of the plants (Tripathi and Kumar, 2007).

3.3.17. Anthelmintic activity *in vitro*

The anthelmintic activity of EtOAc, MeOH and aqueous crude extracts of leaves on the Indian adult earthworm, *Pheretima posthuma* was reported by Gadamsetty *et al.* (2013b). All *D. sepiaria* extracts tested exhibited concentration-dependent activity of 10-80 mg/mL. The aqueous extract was significantly active causing paralysis after 72.2 min at 20 mg/mL, 42.3 min at 40 mg/mL, 12.6 min at 60 mg/mL and 8.3 min at 80 mg/mL; death occured after 148.5 min at 20 mg/mL, 101.3 min at 40 mg/mL, 30.7 min at 60 mg/mL and 14.0 min at 80 mg/mL. For comparison, 10 mg/mL of the standard reference drug, piperazine citrate, showed paralysis after 23.4 min and death after 63.2 min.

3.3.18. Toxicity

The stem bark and seed extracts of *D. roxburghii* revealed significant toxicity in the *Artemia salina* lethality assay, with LD_{50} values of 1.175 µg/mL and LC_{50} 427.74 µg/mL, respectively (Krishnaraju *et al.*, 2005, Raghavendra *et al.*, 2010). The 70 % v/v MeOH extract of dried *D. roxburghii* leaves and stems showed acute toxicity (LD_{50} 500 mg/kg) in female Wistar albino rats following oral adminsitration (Rajahamsa *et al.*, 2013). Awasthy *et al.* (2000) reported the effects of orally administered *D. roxburghii* leaf extract to young weaning Swiss albino mice at 0.5, 1.0 or 2.0 g/kg /day for seven consecutive days. The results demonstrated that the leaf extract induced significant mitosis-disruptive chromosomal changes in bone marrow cells, although there were no changes in the incidence of structural abnormalities among metaphase chromosomes. It was proposed that the extract might have interferred with the spindle and other related proteins causing polyploidy, aneuploidy, c-mitosis, *etc*. Single oral doses (4 -12 g/kg) of *D. gossweileri* stem bark extracts of produced acute toxicity in rats, but did not result in mortality or significant behavioural and biochemical changes. In subacute toxicological studies with both male and female rats, orally administered bark extract (48 hourly dosing of 500 mg/kg or 1000 g/kg for 4 weeks) did not cause any changes in biochemical or haematological parameters. There were no indicators of toxicity in terms of feeding or body weight alterations, with the exception of 1000 mg/kg dosed male rats

observed to have slightly decreased body weight. Morphological examination of various organs and fluctuations in their relative weights revealed no differences between control groups (treated with distilled water or maize oil) and treated rats (Ngouana *et al.*, 2010). Moreover, no toxic effect was noticed in male and female albino Wistar rats treated per os with the crude stem bark extract at a dose up to 12 g/kg of body weight (Ngouana *et al.*, 2011).

3.4. Correlation of traditional medicinal use with bioactivity of crude extracts and isolated compounds

Traditional medicinal use of *D. chevalieri*, *D. gerrardii*, *D. gossweileri*, *D. natalensis* as well as *D. roxburghii* showed a clear correlation with significant bioactivities found *in vivo* and/or *in vitro* against malaria, cancers, pain, and rheumatism (table 3). Therefore, chemical and pharmacological investigation of other African traditional medicinal species is recommended for the following parts of plant which are preferrently applied for medicinal preparations. Among the 19 *Drypetes* species studied, only 5 were biologically tested according to the traditional uses of the plant. This may be due to the lack of appropriate equipment for biological tests or because the plants were studied separately by a chemist, a pharmacologist or a biologist. This is why the interdisciplinary approach (biologist, phytochemists and pharmacologist) should be followed, to conduct a comprehensive research work on any species.

Table 3: Correlation traditional medicinal use of plants from the family Putranjivaceae with bioactivities *in vitro* and *in vivo*

Plant name	Traditional medicinal use	Bioactivity of compounds and extract related to the traditional use	References
Drypetes chevalieri	Unspecified parts of the plant are used in Cameroon for the treatment of tumors	putanjivadione **8** isolated from the stem was active against hepatocellular carcinoma cell line BEL7402, human lung cancer cell line A549 and leukemia cell line HL60.	Dalziel and Hutchinson, 1937; Bouquet and Debray, 1974; Wansi et al., 2006, 2007; Chen *et al*., 2014
Drypetes gerrardii	Unspecified parts of the plant are used for the treatment of malaria among 'Chonyi' people in Kilifi District, Coast province, Kenya	resinone **66**, drypetenone D **92** and E **93** showed significant *in vitro* antiplasmodial activity and not toxic against rat myoblast cell line L6. Drypetenone D **92** not active in *Plasmodium berghei* mouse model	Ng′ang′ a et al., 2011, 2012; Hata et al., 2014
Drypetes gossweileri	The bark is used in Western Africa for the treatment of pain	Extract displayed significant analgesic activity in animal models, and was not toxic in animal model as well	Bouquet, 1969; Burkill, 1985; Muganza et al., 2012; Ngouana *et al*., 2010, 2011; Bomba *et al.*, 2013
Drypetes natalensis	Unspecified parts of the plant are used for the treatment of malaria in Tanzania	The stem bark and root extracts were antiplasmodial *in vitro* and not toxic against rat myoblast cell line L6	Gessler et al., 1995; Malebo et al., 2009

Drypetes roxburghii	A paste composed of the seeds is applied in India to the forehead for the treatment of pain	The seed extract showed relief of pain in animal model; the seed extract was not toxic against *Artemia salina*	Sudharshan et al., 2009; Kumar, 2012; Kadir et al., 2013; Raghavendra *et al.*, 2010
	Leaves and another parts are used in India in the treatment of rheumatism and inflammation	The extract showed reduction of inflammation in animal models, however, the leaf extract displayed acute oral toxicity and induced mitosis-disruptive chromosomal changes in bone marrow cells	Chopra *et al*., 1970b; Awasthy *et al.*, 2000; Sudharshan *et al.*, 2009; Reanmongkol *et al*., 2009; Pandey and Tripati, 2011; Kaushik *et al.*, 2012; Kumar, 2012; Rajahamsa *et al.*, 2013

4. Conclusions

The genus *Drypetes* has been used in the Subsaharan African and Asian traditional medicines to treat a multitude of disorders, like microbial infections, malaria, inflammation, tumours, as well as for the treatment of wounds, headache, and urethral problems. Some *Drypetes* species are used to protect food against pests, as an aphrodisiac, a stimulant/depressant, a rodenticide and a fish poison, against insect bites, to induce conception and for general healing. From 19 *Drypetes* species, a total of 142 different compounds belonging to more than 10 classes of natural compounds, including triterpenoids (76) (friedelane (35), oleanane (22), lupine (16) and hopane-type (3)), sesquiterpenoids (11), dinorditerpenoids (10), phenylpropanoid-phenylethanoid (9), lignans (8), steroids (7), flavonoids (6), xanthone (1), anthraquinone (1) as well as some thiocyanates (5) and other metabolites (8), had been isolated. Triterpenoids, especially the friedelane derivatives were the only class of compound isolated in all 19 species. 10 pimarane dinorditerpenoids were isolated from the species collected in Asia *D. littoralis* (Taiwan), *D. perreticulata* (China), and in Africa *D. gerrardii* (Kenya), *D. gossweileri* (Cameroon). These compounds with aromatic ring C were exclusively isolated from this genus and might turn out to be good candidates for chemotaxonomic markers. Several crude extracts of these plants, and isolated compounds displayed significant analgesic, anthelmintic, antidiabetic, anti-emetic anti-inflammatory, antioxidant, antiparasitic, central nervous system depressant, cytotoxic, and insecticidal activities both *in vitro* and *in vivo*. But, concerning the safety of traditional medicines derived from *Drypetes*, it should be noted that some crude extracts showed significant toxicity in *Artemia salina* model and in female Wistar albino rat, in addition, some extracts induced mitosis-disruptive chromosomal changes in the bone marrow cells of Swiss albino mice. Moreover, the flavonoid amentoflavone (**128**) reported from the extracts of genus *Drypetes* showed high toxicity against L-1-rat skeletal myoblast cells. Most of the *Drypetes* genus used in tradional medicine has never been investigated for their toxicity; therefore, doses given by the traditional healers might result in increased health problems or even death. As a consequence, traditional medicine from this genus should in future be applied with care. Further toxicological studies on the genus are urgently needed to improve their safety in traditional medicinal applications. Nevertheless, it is suggested that

dinorditerpenoids might play an important biologic role within the genus *Drypetes*. These compounds displayed very significant antimalarial activity *in vitro* against chloroquine-resistant African *Plasmodium falciparum* NF54 with IC_{50} of 0.9 µM, as well as significant cytotoxic activity against the leukemia cell line HL60 with IC_{50} of 1.95-1.37 µM. Further bioactivity testing of these compounds is recommended. Among the 19 *Drypetes* species, only *D. chevalieri, D. gerrardii, D. gossweileri*, *D. natalensis* as well as *D. roxburghii* showed a clear correlation with significant bioactivities found *in vivo* and/or *in vitro* against malaria, cancers, pain, and rheumatism. This may be due to the lack of appropriate equipment for biological tests in Africa and in Asia or because the plants were studied separately by a chemist, a pharmacologist or a biologist. It's why the interdisciplinary approach is recommend (biologist, phytochemists and pharmacologist) to conduct a comprehensive bioassay-guided fractionation of not yet examined species.

Conflict of interest

The authors declare no conflict of interest

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