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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.*, *D. 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 literatures 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 higher toxicity of some crude extracts. Interestingly, this review also reports 10 pimarane dinditerpenoids 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 tissue, a compound they share with the genus *Putranjiva* in this family and because it 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/documentated 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 coriaceous 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 hypogynous 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).](image)

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 interrogated (*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 distributed 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
<table>
<thead>
<tr>
<th>Name of species</th>
<th>Country/Province</th>
<th>Ethnomedicinal uses</th>
<th>Type of recipe</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>D. aubrévillei</em></td>
<td>Guinea, Liberia, Ghana and Ivory Coast</td>
<td>Healing on the skin and mucosa</td>
<td>Bark and fruit</td>
<td>Burkill (1985)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary disorders and analgesic</td>
<td>Bark</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liberia</td>
<td>Fever, rheumatism and general fatigue</td>
<td>Decoction of macerated bark and fruit</td>
<td>Cooper and Record (1931)</td>
</tr>
<tr>
<td></td>
<td>Elsewhere</td>
<td>Blotchy skin, locally as “dishcloth”</td>
<td>Powdered stem bark</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expectorant and bronchial decongestant</td>
<td>Pap made from the bark</td>
<td>Bouquet and Debray (1974)</td>
</tr>
<tr>
<td><em>Drypetes capillipes</em></td>
<td>Central African countries</td>
<td>General analgesia</td>
<td>Leaves and bark</td>
<td>Burkill (1985)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical massage for stiffness of the neck</td>
<td>Leaves</td>
<td></td>
</tr>
<tr>
<td><em>Drypetes chevalieri</em></td>
<td>Cameroon</td>
<td>Tumours, swellings, inflammation and gonorrhoea</td>
<td>Whole plant</td>
<td>Dalziel and Hutchinson, (1937); Bouquet and Debray (1974)</td>
</tr>
<tr>
<td>Beille ex Hutch. &amp; Dalziel</td>
<td>‘Kru’ and the Guere of Liberia</td>
<td>Dysesthy</td>
<td>Sap expressed from leaves and twigs</td>
<td>Kerharo and Bouquet (1950)</td>
</tr>
<tr>
<td></td>
<td>Ivory Coast</td>
<td>head-colds and sinusitis</td>
<td>Powdered leaves</td>
<td></td>
</tr>
<tr>
<td></td>
<td>West tropical Africa</td>
<td>Intestines; pulmonary troubles and naso-pharyngeal affections</td>
<td>Leaves</td>
<td>Burkill (1985)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhoea and dysentery</td>
<td>Sap expressed from leaves and twigs</td>
<td></td>
</tr>
<tr>
<td><em>Drypetes gerrardii</em></td>
<td>Coast province, Kenya</td>
<td>Malaria and other ailments</td>
<td>Unspecified parts</td>
<td>Ng'ang' a et al. (2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analgesia, vermutinge, genital stimulant/depressant, against veneral diseases, as febrifuge, reptile-repellent, and as fish-poison</td>
<td>Bark</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Western Cameroon</td>
<td>gonorrhoea and toothache</td>
<td>Bark</td>
<td>Dalziel and Hutchinson, (1937)</td>
</tr>
<tr>
<td></td>
<td>Central African Republic</td>
<td>Helminthic diseases, rheumatism, fever and malaria</td>
<td>Unspecified parts</td>
<td>Ngoupayou et al. (2003); Ichinda and Sob, (2008); Raponda-Walker and Sillans (1961)</td>
</tr>
<tr>
<td></td>
<td>Poison fishing</td>
<td></td>
<td>Bark and fruit</td>
<td>Raponda-Walker and Sillans (1961)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatism, headaches, general pain, body-pains, helminths and filariasis</td>
<td>Bark</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wounds and for toothache</td>
<td></td>
<td>Roots</td>
<td>Troupin (1982)</td>
</tr>
<tr>
<td></td>
<td>Poison fishing</td>
<td></td>
<td>Bark and fruit</td>
<td>Raponda-Walker and Sillans (1961)</td>
</tr>
<tr>
<td></td>
<td>Congo (Brazzaville)</td>
<td>Vermifugal enema</td>
<td>Bark-macerate or decoction with pepper</td>
<td>Bouquet (1969)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urethral discharge or as an aphrodisiac</td>
<td>Bark powder is cooked together with bananas</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever in young children</td>
<td>Powder-decoction is added to bath water</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repel snakes</td>
<td>Boiled bark water</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antipyretic, analgesic, aphrodisiac, for body pain, headache and urethreal problems</td>
<td>Bark</td>
<td></td>
</tr>
</tbody>
</table>
An overview on the occurrence and traditional use of this plant 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).


*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).


*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 “pilpili” 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 venereal diseases, as febrifuge, reptile-repellent, and as fish-poison (Burkill, 1985). In Western Cameroon, the bark is administered 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 anthelmintic, 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 of 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 anthelmintic (Raponda-Walker and Sillans, 1961).
3.1.8. *Drypetes natalensis* (Harv.) Hutch; synonym: *Drypetes natalensis* var. *natalensis*

*D. 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

*D. 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.

*D. 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), (2S) 1-thio-β-D-glucopyranose-N-(sulfooxy)-sec-butylanimidoyl (glucojiaputin, 2) and its isomer (2R) 1-thio-β-D-glucopyranose-N-(sulfooxy)-sec-butylanimidoyl (glucocochlearin, 3) from the steam volatile oil of wet kernels of the Asian *D. roxburghii*. In addition, two glucoside compounds, (2S) 1-thio-β-D-glucopyranose-N-(sulfooxy)-2-hydroxymethylbutylisothiocyanate (glucocleomine, 4) and (2S) 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](image)

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, 3β-acetoxy cycloart-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).

![Figure 3. Structures of compounds 6 and 7](image)

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. liitoralis* (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 3β-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-3β-ol (17), its stereoisomer epifriedelanol (18), epifriedelanol methyl ether (19) and 5β,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-3α,16β-diol (21), its isomer friedelane-3β,29β-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 Cameroonian species *D. paxii* and *D. inaequalis* as well as the two Asian species *D. hoanensis* Gagnep. and *D. roxburghii*, four compounds were isolated, namely 12α-hydroxyfriedelanel3,15-dione (24), 3β-hydroxyfriedelan-25-al (25), 3α-hydroxyfriedelan-7-one (26), 3α-hydroxyfriedelan-12-one (27), 3α-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 3α-hydroxy-25-nor-friedel-9(11)ene (37) and putralone or 10α-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 3α-(E)-caffeoyloxyfriedelan-7-one (39) and 3α-(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. $R_1 = R_3 = R_4 = H_2; \ R_2 = O$

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. $R_1 = H; \ R_2 = O; \ R_3 = H$
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 3β-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 28β-D-glucopyranosyl-30-methyl-3β-hydroxyolean-12-en-28,30-dioate (50) along with serranic acid (51), 28β-D-glucopyranosyl-3β-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), 3β,22β-dihydroxyolean-12-en-28-oic acid (55), and chikusetsusaponin IVa methyl ester (56) were isolated. Furthermore, the EtOH/H₂O (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 3β-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-3β-ylcaffeate (60) (Wansi et al., 2006). From the MeOH extract of the stem bark of *D. tessmanniana*, a 3β-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).
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. \( R_1 = H; \ R_2 = OH; \ R_3 = CH_3; \ R_4 = CH_2OH \)

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. \( R_1 = OH; \ R_2 = CH_3 \)

57. \( D-Glc-L-Rha-L-Ara \)
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$_2$O 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-3β,6α-diol (67) and 3β-acetoxylup-20(29)-en-6α-ol (68) (Awanchiri et al., 2009). From the MeOH extract of the stem bark of *D. tessmanniana*, 3β,6α-dihydroxyxylup-20(29)-en (69) was isolated (Dongfack et al., 2008). From twigs and leaves of *D. perreticulata* extracted with EtOH/H$_2$O (95/5) messagenic acid D (70) and G (71), betulonic acid (72), 2α,3α-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$_2$O extract of the stems of *D. congestiflora* (Chen et al., 2015). Furthermore, four caffeoylllupane derivatives were isolated from this genus, namely 3β-caffeoylbetulinic acid (75) from

![Figure 5. Structures of compounds 41-62](image-url)
the stems of *D. congestiflora* (Chen et al., 2015), 3β-caffeoyloxylup-20(29)-en-6α-ol (76) from the air-dried stems and ripe fruit of *D. inaequalis* (Awanchiri et al., 2009) and two isomers betulin-3β-(Z)-caffeate (77) and betulin-3β-(E)-caffeate (78) from twigs and leaves of *D. perreticulata* Gagnep. (Ge et al., 2014).

![Figure 6](image-url)

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

![Figure 7. Structures of compounds 79-81](image)

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, 3β-hydroxysigmasta-5,22-dien-7-one (88) was isolated from the DCM extract of the roots of *D. hoaensis* (Wittayalai *et al.*, 2014).
3.2.3. Diterpenes

Ten dinorditerpenoids belonging to the pimarane class with the armoricat 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 10S-12-hydroxy-11-methoxy-13-methylpodocarpa-1,5,8,11,13-pentaene-3,7-dione (89), drypetenone B or 10S-12-hydroxy-11-methoxy-13-methylpodocarpa-5,8,11,13-tetraene-3,7-dione (90), and drypetenone C or 10S-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$_2$O (95/5) afforded dryperrein A or (10S)-11,12-dihydroxy-6-methoxy-15,16-dinorpimara-5,8,11,13-tetraene-3,7-dione (95), dryperrein B or (10S)-6,11,12-trihydroxy-15,16-dinorpimara-5,8,11,13-tetraene-3,7-dione (96), dryperrein C or (10S)-11,12-dihydroxy-6-methoxy-15,16-dinorpimara-1,5,8,11,13-pentaene-3,7-dione (97), and dryperrein D or (10S)-6,11,12-trihydroxy-15,16-dinorpimara-1,5,8,11,13-pentaene-3,7-dione (98) (Ge *et al.*, 2014).
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 hoaensibenofuranal (103),...
hoaensieudesone (104), hoaensifuranonal (105), hoaensieremione (107) and the known compound warburgin (108) from 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).

![Chemical structures](image.png)

**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 drypeararmoracein 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).
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).
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 drypeararmoracein 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).

**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 CHCl₃-soluble fraction of the leaves of *D. hieranensis* afforded the known tannin hexamethoxyellagic acid (139) (Chen *et al.*, 1999) (Fig. 14).
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-7R,8S-epoxy-octadecane (142), also a pheromone of the gypsy moth (Sun *et al.*, 2014) (Fig. 15).

From *D. roxburghii* seeds, a multifunctional ~12 kDa heterodimeric protein named putrin belonging to 2S 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 compounds.
<table>
<thead>
<tr>
<th>Plant name</th>
<th>Part of plant</th>
<th>Isolated compound / crude extract</th>
<th>Reported bioactivity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>D. chevalieri</em></td>
<td>stem</td>
<td>furanoeudesm-1-on-13-oic acid 100</td>
<td>Antileishmanial</td>
<td>Wansi <em>et al</em>., 2007</td>
</tr>
<tr>
<td><em>D. congestiflora</em></td>
<td>stem</td>
<td>hoaensieremone 107</td>
<td>Active against human lung adenocarcinoma cell line A549 and murine mouse melanoma cell line B16 F10</td>
<td>Chen <em>et al</em>., 2015</td>
</tr>
<tr>
<td><em>D. gerrardii</em></td>
<td>crude extract</td>
<td>resinone 66</td>
<td>Antiplasmodial and not toxic against rat myoblast cell line L6</td>
<td>Ng’ang’a <em>et al</em>., 2011; 2012</td>
</tr>
<tr>
<td></td>
<td>stem</td>
<td>5β,24-cyclofriedelan-3-one 20</td>
<td>Antiplasmodial and mild toxic against rat myoblast cell line L6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>drypetenone D</td>
<td>92</td>
<td>Antiplasmodial, antileishmanial, antitrypanosomal, not toxic against rat myoblast cell line L6 and not active in <em>Plasmodium berghei</em> mouse model</td>
<td>Hata <em>et al</em>., 2014;</td>
</tr>
<tr>
<td></td>
<td>drypetenone E</td>
<td>93</td>
<td>Antiplasmodial, antileishmanial, antitrypanosomal and not toxic against rat myoblast cell line L6</td>
<td></td>
</tr>
<tr>
<td>leaves</td>
<td>crude extract</td>
<td>putranoside A 62</td>
<td>Antitrypanosomal</td>
<td></td>
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<tr>
<td><em>D. gossweileri</em></td>
<td>stem bark</td>
<td>crude extract</td>
<td>Antibacterial, antifungal and not toxic in animal experiment</td>
<td>Ndonoua <em>et al</em>., 1991; Ijah and Ojebanji, 2003; Tan <em>et al</em>., 2006; Ngouana <em>et al</em>., 2010; 2011</td>
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<td></td>
<td></td>
<td>β-amyrone 43, N-β-D-glucopyranosyl-p-hydroxyphenylacetamide 117</td>
<td>Antifungal</td>
<td>Matochko, 2010; Ata <em>et al</em>., 2011</td>
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<tr>
<td></td>
<td>cork</td>
<td>essential oil</td>
<td>Antifungal</td>
<td>Ndonkeu <em>et al</em>., 2013</td>
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<tr>
<td></td>
<td>bark</td>
<td>stearic acid 140</td>
<td>Active against human hepatoma cell lines HepG2 and Hep3B; low toxic against human normal cell line</td>
<td>Dupont <em>et al</em>., 1997; Tang <em>et al</em>., 2007</td>
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<tr>
<td></td>
<td></td>
<td>not reported maslinic acid 49</td>
<td>Antidiabetic</td>
<td>Sow <em>et al</em>., 1994; Hou <em>et al</em>., 2009</td>
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<td></td>
<td>bark</td>
<td>N-β-D-glucopyranosyl-p-hydroxyphenylacetamide 117, β-amyrone 43</td>
<td>Antidiabetic</td>
<td>Matochko, 2010; Ata <em>et al</em>., 2011</td>
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<td>stem bark</td>
<td>crude extract</td>
<td>Analgesic in animal experiment</td>
<td>Bomba <em>et al</em>., 2013</td>
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<td></td>
<td>bark</td>
<td>N-β-D-glucopyranosyl-p-hydroxyphenylacetamide 117</td>
<td>Acetylcholinesterase inhibition,</td>
<td>Matochko, 2010; Ata <em>et al</em>., 2011</td>
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<td>Species</td>
<td>Plant Part</td>
<td>Compound Name</td>
<td>Activity</td>
<td>Reference</td>
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<td><em>D. hainanensis</em></td>
<td>stems + leaves</td>
<td>crude extract</td>
<td>Insecticidal against <em>Sitophilus zeamais</em> and <em>Rhyzopertha dominica</em></td>
<td>Aba et al., 2013</td>
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<tr>
<td></td>
<td>leaves</td>
<td>hainanenone 34</td>
<td>Active against human hepatoma cell line BEL7402, human lung adenocarcinoma</td>
<td>Chen et al., 2011; 2014</td>
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<td></td>
<td></td>
<td>drypetesin A 112, drypetesin B 113, drypetesin C 114</td>
<td>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</td>
<td>Zhang et al., 2015</td>
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<td><em>D. hoaensis</em></td>
<td>roots</td>
<td>(E)-caffeyloxyfriedelan-7-one 39, 3α-(E)-p-coumaroyloxyfriedelan-7-one 40, 3β-hydroxyfriedelan-12-one 27 hoaensifuranonal 105, hoaensieremodione 106, hoaensieremone 107</td>
<td>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</td>
<td>Wittalai et al., 2014</td>
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<tr>
<td><em>D. inaequalis</em></td>
<td>stem</td>
<td>lup-20(29)-en-3β,6α-diol 67</td>
<td>Antibacterial</td>
<td>Awanchiri et al., 2009</td>
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<td>ripe fruit</td>
<td>28β-D-glucopyranosyl-30-methyl-3β-hydroxyolean-12-en-28,30-dioate 50</td>
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<td><em>D. laciniata</em></td>
<td>whole stem, stem</td>
<td>3β-hydroxyfriedelane-7,12,22-trione 16, chikusetsusaponin Iα methyl ester 56</td>
<td>Antibacterial</td>
<td>Fannang et al., 2011</td>
</tr>
<tr>
<td><em>D. littoralis</em></td>
<td>stem</td>
<td>crude extract</td>
<td>Antiviral and against Epstein Barr virus DNA polymerase</td>
<td>Chiou, unpublished study</td>
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<td></td>
<td></td>
<td>amentoflavone 127</td>
<td>Antiplasmodial and toxic against rat myoblast cell line L6</td>
<td>Lin et al., 2001; Ng'ang'a et al., 2012</td>
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<td><em>D. molunduana</em></td>
<td>stem bark</td>
<td>crude extract</td>
<td>Analgesic and antiinflammatory in animal experiment</td>
<td>Wandji et al., 2000; Nke et al., 2001; 2003</td>
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<tr>
<td></td>
<td></td>
<td>drypemolundein A 99</td>
<td>Antiinflammatory and analgesic in animal experiments</td>
<td></td>
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<td></td>
<td>oleanolic acid 48</td>
<td>Antidiabetic</td>
<td>Hou et al., 2009</td>
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<tr>
<td><em>D. natalensis</em></td>
<td>bark, root</td>
<td>crude extract</td>
<td>Antitrypanosomal, antileishmanial, antiplasmodial and not toxic against rat myoblast cell line L6</td>
<td>Malebo et al., 2009</td>
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<tr>
<td><em>D. paxii</em></td>
<td>stems</td>
<td>12β-hydroxyfriedelane-3,15-dione 24, 3β-hydroxyfriedelane-25-al 25, friedelin 13, friedelan-7-one 14 and 28β-D-glucopyranosyl-3β-</td>
<td>Antibacterial</td>
<td>Chiozem et al., 2013</td>
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<td>Species</td>
<td>Plant Part(s)</td>
<td>Extract Form</td>
<td>Activity</td>
<td>Reference(s)</td>
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<tr>
<td><em>D. perreticulata</em></td>
<td>twigs and leaves</td>
<td>crude extract</td>
<td>Antibacterial and broad spectrum cytotoxic activity</td>
<td>Chen et al., 2012</td>
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<td></td>
<td>dryperrein D 98 Antifungal</td>
<td>Ge et al., 2014</td>
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<td></td>
<td>crude extract</td>
<td>Active against human lung tumor cell line A549 and leukemia cell line HL60</td>
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<td><em>D. roxburghii</em></td>
<td>seeds</td>
<td>putrin</td>
<td>Antibacterial, DNase and RNase inhibition and antifungal</td>
<td>Tomar et al., 2014</td>
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<td></td>
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<td>crude extract</td>
<td>Not toxic against <em>Artemia salina</em></td>
<td>Raghavendra et al., 2010</td>
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<td>stem bark</td>
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<td>Highly toxic against <em>Artemia salina</em></td>
<td>Krishnaraju et al., 2005</td>
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<td>fruits</td>
<td>nanoparticles of metallic silver</td>
<td>Antiplasmodial, not toxic against the fish <em>Poecilia reticulata</em></td>
<td>Haldar et al., 2013</td>
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<tr>
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<td>leaves</td>
<td>crude extract</td>
<td>Antibacterial and antifungal</td>
<td>Kumar et al., 2006</td>
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<td>leaf + fruit</td>
<td></td>
<td>Antifungal</td>
<td>Kuri et al., 2010, 2011</td>
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<td>leaf</td>
<td>essential oil</td>
<td>Antifungal</td>
<td>Tripathi and Kumar, 2007; 2013; 2014a; 2014b; Pandey and Tripathi, 2011</td>
</tr>
<tr>
<td></td>
<td>bark</td>
<td>crude extract</td>
<td>Active against human hepatocellular carcinoma cell line HepG2 and low toxic against <em>Artemia salina</em></td>
<td>El-Manawaty et al., 2013</td>
</tr>
<tr>
<td></td>
<td>trunc bark</td>
<td>putanjivadione 8</td>
<td>Active against hepatocellular carcinoma cell line BEL7402, human lung cancer cell line A549 and leukemia cell line HL60</td>
<td>Garg and Mitra, 1968; Chen et al., 2014</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>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)</td>
<td>Varma et al., 2010; Rajahamsa et al., 2013; Awashthy et al., 2000</td>
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<td></td>
<td>Central nervous system depressant activity in animal model; not toxic against <em>Artemia salina</em></td>
<td>Sudharshan et al., 2009; Raghavendra et al., 2010</td>
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<td></td>
<td></td>
<td></td>
<td>Antioxidant</td>
<td>Chinmaya et al., 2009</td>
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<td></td>
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<td></td>
<td>Shahwar et al., 2012</td>
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<td></td>
<td>Rajahamsa et al., 2013</td>
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<td></td>
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<td></td>
<td>Anti-inflammatory in animal experiment (ether, acetone, MeOH); acute oral toxicity in animal experiment (70% MeOH extract)</td>
<td>Reanmongkol et al., 2009; Kaushik et al., 2012; Rajahamsa et al., 2013</td>
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<td>Analgesic in animal experiment</td>
<td>Reanmongkol et al., 2009; Sudharshan et al., 2009</td>
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<td></td>
<td></td>
<td></td>
<td>Inhibition of bovine trypsin in a 1:1 molar ratio</td>
<td>Chaudhary et al., 2008</td>
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</table>
3.3.1. Antileishmanial and antitypansomal 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\textsubscript{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\textsubscript{50} 7.8 µM and 14.0 µM, respectively compared to the positive control (miltefosine IC\textsubscript{50} of 0.552 µM). The same solvent extract of the leaves showed moderate activity against *Trypanosoma brucei rhodesiense* STIB 900 strain, with IC\textsubscript{50} 12.1 mg/mL, while the same isolated compounds showed weak activity against *Trypanosoma brucei rhodesiense* with IC\textsubscript{50} 18.0 µM and 6.0 µM, respectively compared to the positif control (melarsoprol IC\textsubscript{50} of 0.003 µM) (Hata et al., 2014). Malebo et al. (2009) reported the antileishmanial and antitypansomal activities of the ethanolic stem and the root bark extracts of *D. natalensis* against *Trypanosoma brucei rhodesiense* STIB 900 with IC\textsubscript{50} 10.70 µg/mL and against *Leishmania donovani* MHOM-ET-67/82 with IC\textsubscript{50} 19.0 µg/mL for the stem bark, and with IC\textsubscript{50} 12.10 µg/mL against *Trypanosoma brucei rhodesiense* STIB 900, and IC\textsubscript{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\textsubscript{50} 40.0 µg/mL compared to the positive control pentamidine with IC\textsubscript{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 antitypansosomal drugs, subject to careful toxicity studies employing human normal cell lines and toxicity tests in animal model.

### Table 3.3.1

<table>
<thead>
<tr>
<th>Species</th>
<th>Source</th>
<th>Extract</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>D. sepiaria</em></td>
<td>leaves</td>
<td>crude extract</td>
<td>Active against cervical cancer cell line SiHa; antiinflammatory in animal experiment, antioxidant and anthelmintic against <em>Pheretima posthuma</em></td>
<td>Gadamsetti et al., 2013a; 2013b</td>
</tr>
<tr>
<td><em>D. tessmanniana</em></td>
<td>stem bark</td>
<td>3β-O-(E)-3,5-dihydroxycinnamoyl-11-oxo-olean-12-ene 61 and 3β,6α-dihydroxylup-20(29)-ene 69</td>
<td>Antibacterial, not active against <em>Candida albicans</em> LMP709U and <em>Microsporum audouinii</em> LMP725D</td>
<td>Dongfack et al., 2008; Kuete et al., 2010</td>
</tr>
</tbody>
</table>

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, 5β,24-cyclofriedelan-3-one 20 isolated from the EtOAc extract of the stem of *D. gerrardii*, exhibited 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 enterocolitica*, *Enterobacter cloacae* and *Salmonella* sp. (Ndouga et al., 1991). The aqueous and ethanolic extracts of the stem bark clearly inhibited *S. aureus*, *Pseudomonas aeroginosa*, *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 against *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 activity 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/H2O (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 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 LD50 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 gonorrhea (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 langeronii*, *M. gypseum*, *Trichophyton rubrum*, *T. mentagerophytes* and *Aspergillus flavus* resulting in MICs 24.41, 48.84, 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-β-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 might be due to the presence of a *N*-glucose moiety in compound 117 (Matlochko, 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 api* by 100% (Ndonkeu *et al*., 2013). Dryperren D 98 isolated from the twigs and leaves of the EtOH/H₂O (95:5) extract of *D. perreticulata* displayed antifungal activity against *C. albicans* ATCC 1600 and *Saccharomyces sake* ATCC 26421 strains 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 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 MI 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 Rhinopus nigricans, P. chrysogenum, P. glabrum and P. oxalicum. Moreover, the fungitoxicity was not destroyed by autoclaving and storage upto 120 days (Pandey and Tripathi, 2011; Kumar, 2013, 2014a, 2014b). Interestingly, a multifunctional ~12 kDa heterodimeric protein named putrin reported from the seeds displayed an IC\textsubscript{50} value of 34.7 μM against A. flavus (Tomar et al., 2014). Compounds, \(3β-O-(E)-3,5\)-dihydroxycinnamoyl-11-oxo-olean-12-ene \(61\) and \(3β,6α\)-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\textsubscript{2}O 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\textsubscript{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\textsubscript{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 hepatoma cell line BEL7402, human lung adenocarcinoma cell line A549, and human leukemia cell line HL60 at the concentration of 10\textsuperscript{-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\textsubscript{50} values of 5.6, 8.2 and 6.7 μM for drypetenin A \(112\), 12.2, 9.4 and 12.5 μM for drypetenin B \(113\) and 14.8, 12.4 and 10.8 μM for drypetenin 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 \(39\), 3α-
(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 spectrum 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, putranjivadione 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 \(\mu\)g/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 \(\alpha\)-glucosidase inhibition with an IC\(_{50}\) value of 5.52 respectively 6.29 \(\mu\)g/mL (Hou et al., 2009). Compound, \(N\)-\(\beta\)-glucopyranosyl-\(p\)-hydroxyphenyl acetamide 117, isolated from the methanolic extract of the bark of *D. gossweileri*, exhibiting high \(\alpha\)-glucosidase inhibitory activity with IC\(_{50}\) 12.0 \(\mu\)M. Acidic hydrolysis afforded its aglycone, which exhibited an \(\alpha\)-glucosidase inhibition activity with an IC\(_{50}\) 60.0 \(\mu\)M suggesting that the higher potency of compound 117 was due to the presence of an \(N\)-glucose moiety (Matchoko, 2010; Ata et al., 2011). In addition, \(\beta\)-amyrone 43 exhibited \(\alpha\)-glucosidase inhibition with an IC\(_{50}\) value of 12 \(\mu\)M (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) inhibition 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 carrageenan 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$_2$O (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$_2$O$_2$ 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 (Matchock, 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-dependerent 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

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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 against 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 occurred 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 administration (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 interfered 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*

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

| 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 |

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### 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, antiemetic 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 traditional 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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