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Ethno medical uses, phytochemistry and pharmacology of *Dianella ensifolia* (Linnaeus) de Candolle: A systematic review

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Abstract

Dianella ensifolia has potential as a source of herbal medicine. The objective of this review is to make an overview of the current knowledge available on the ethno medical uses, phytochemistry and pharmacology of *D. ensifolia*. *Dianella ensifolia* is used traditionally in many areas of the world as herbal medicine, especially as topical medicines for ferunculosis, abscesses, lymphangitis, tuberculosis lymphadenitis, tinea, traumatic injuries, and wounds. The plant can also be taken internally in the treatment of dysentery, dysuria, leucorrhoea, blanorrhoea, and fatigue. The phytochemical constituents are belonging to phenolic compounds, quinones, flavans, cycloartane-type triterpenoids, steroids, chromones, water soluble carbohydrates, glycosides. The preclinical data are reported for, antioxidant activities, antibacterial, antiviral, anti-inflammation, tyrosinase inhibition. Ethno medical uses of *D. ensifolia* indicates that aerial and roots are good source of herbal medicine. Phytochemical constituents of aerial and roots are complex with various bioactivities. Pharmacologically, *D. ensifolia* show its potential as antioxidant, antimicrobial, antiviral, wound healing medicine, and anti melanogenesis.

Keywords: Cerulean flax-lily, *dianella ensifolia*, *dianella nemorosa*, *dianella parvilora*, prakepey, sword-leaf draceana

Introduction

Dianella (flax lilies) is a monocotyl genus of flowering plants, the largest genus in Hemerocallidaceae with at least 20 different species. In Papua-Indonesia, it is called Pra Kepai or Tegari. *D. ensifolia* has several synonyms, *D. ensata*, *D. nemorosa*, *D. parvilora*, and *D. sandwicensis*. *D. ensifolia* has an attractive foliage and shiny, blue to purple berries [1, 2]. *D. ensifolia* is used traditionally as herbal medicine in subtropical and tropical countries. Its current status should be evaluated in order to direct and push future research activities. Therefore, its potential as herbal medicine for various diseases should be explored and developed through preclinical as well as clinical trials. The literature study on its ethno medical uses, phytochemistry and pharmacology of various preparations is the key cornerstones for the best application. The objectives of this review are to form knowledge from the information available on the ethno medical uses, phytochemistry, and pharmacology of *D. ensifolia*. The obtained information is discussed and compared with those described in ethnobotanical and pharmacological literatures.

2. Methods

Two searching engines used in this study were PubMed and Science Direct. The searching was carried out up to February 4th, 2020 with keyword: *Dianella*. From PubMed and Science Direct, 38 and 261 results were obtained respectively. Inclusion criteria for this study were the relevant articles related to *Dianella* and studies that published in English. 265 irrelevant titles were excluded due to duplication and non English-language studies. There were 34 full text articles that meet systematic review criteria.

3. Ethno medical uses

The importance of the available information on the traditional use of plant species is confirmed, and suggesting the crucial role of ethnobotanical studies for rural development, biodiversity conservation, and the sustainable use of plant resources [3]. Extracts of various parts, roots, seeds, leaves, flowers, and fruits can be carried out through various different extraction methods. Traditional method is infusion, dried material, poultice, ointment, fresh leave, ashes, whole plant. The advantages of modern approaches are reported with regards to traditional ones, in terms of time and solvent consuming and efficiency, such as ultrasonic

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assisted, microwave, pressured fluid and supercritical fluid extraction [4].

The ethno medical uses of *D. ensifolia* can be categorized into two categories, external and internal use. The examples of the external use of *D. ensifolia* are

- poultice of the roots that placed on the abdomen to act as a vermifuge and to treat scrofulous glands.
- ashes of the roots and leaves that applied as an ointment for treating boils, itch, jaundice, herpes sores and rheumatism,
- leaves that applied to wounds,
- whole plant as ingredient that used in a treatment for chronic infections of the skin, and
- whole plant that widely used for treating lymphangitis, tinea and carbuncle sore abscess [5].

The examples of the internal use of *D. ensifolia* are

- Whole plant that taken orally in the treatment of dysentery, dysuria, leucorrhoea and blanorrhoea.
- Stem infusate for treating fatigue, irritating cough and throat mucus [6].
- Dried fibrous roots that chewed as a vermifuge.
- Decoction is drunk for abdominal pains and in case of impotence [7].
- Non malaria remedy extract *D. ensifolia* [8].
- Root, leaf and stem are prepared as Tea in Madagascar;

used for persistent fever and for dysentery [9].

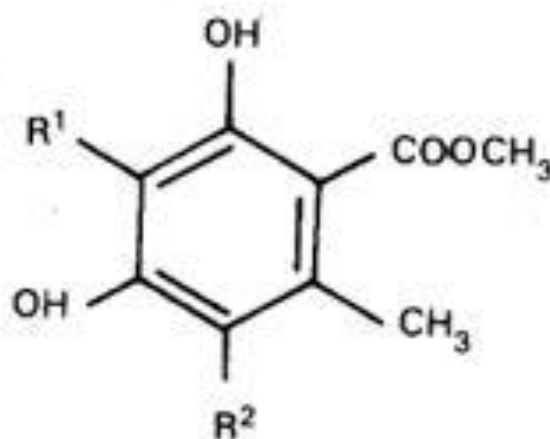
- Whole plant is useful for treatment purgative, stomach aches [10];
- Leaves are used for vertigo, fever, scabies, and skin illness [10].

D. ensifolia is also used for other than medical uses, such as the berries juice for a pale blue dye; the pounded and roasted fresh rhizome that mixed with rice for killing mice and rats; the aromatic rhizome and roots that are ingredients in cosmetics and perfume; and the boiled leaves that used for fumigations.

4. Phytochemistry

4.2 Phenolic compounds

Various types of phenolic are detected in various parts of *D. ensifolia*. Several compounds belong to the simple phenolic compound (C1) and benzenoids, for example dianellidin (syn. musizin), methyl orsellinate, 7-acetyl-4R,8-dihydroxy-6-methyl-1-tetralone, methyl b-orcinolcarboxylate, dianellose and amentoflavone (Figure 1) [11, 12]. Other phenolic compounds are belong to Diarylpropane and flavans (a biflavan, a biflavone, and a tetralone). Example of the most important propane is 1-(2,4-dihydroxyphenyl)-3-(2,4-dimethoxy-3-methylphenyl) propane (UP302) which is a potent inhibitor of tyrosinase [12].



1. R¹ = -CH₃, R² = H
2. R¹ = R² = -CH₃
3. R¹ = R² = -H

Fig 1: Several Phenolic compounds of *D. ensifolia*

1. Methyl 2, 4-dihydroxy-3,6-dimethylbenzoate,
2. Methyl orsellinate,
3. 2, 4-dihydroxy-6-methoxy-3-methylacetophenone

4.2 Flavan/Flavonoids

The aerial and root parts of *D. ensifolia* contain flavans,

named (2S)-2',4'-dihydroxy-7-methoxy-8-methylflavan and (2S)-2'-hydroxy-4',7'-dimethoxy-8-methylflavan, 2(S)-20,40 - dihydroxy-7-methoxyflavan; diaensi-biflavan (5-hydroxy-7,4'-dimethoxy-(6,6''-methylen)-biflavan); 2(S)-7,40 - dimethoxyflavan; and 5,7-dihydroxy-40-methoxyflavan (Table 1, Figure 2) [13, 14, 15].

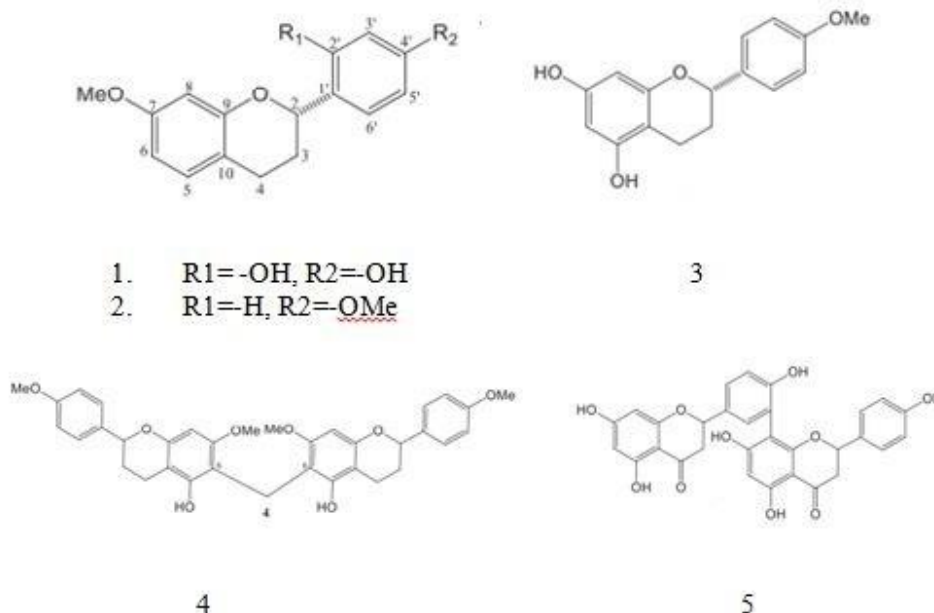


Fig 2: Flavans of *Dianella ensifolia* [14]

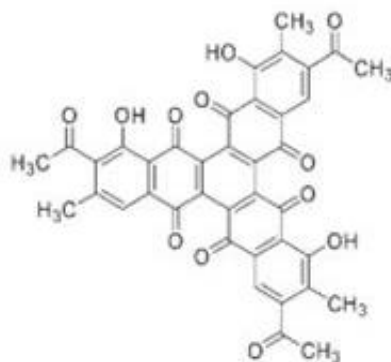
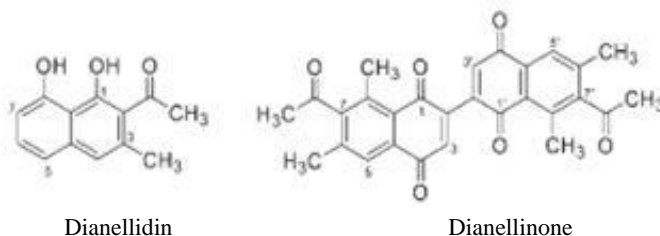
1. 2(S)-20,40-dihydroxy-7-methoxyflavan
2. 2(S)-7,40-dimethoxy flavan
3. 5,7-dihydroxy-40-methoxyflavan
4. diaensi-biflavan (5-hydroxy-7,4'-dimethoxy (6,6''-methylene)-biflavan)
5. amentoflavone

4.3 Quinones

Quinones constitute a structurally diverse class of phenolic compounds with a wide range of pharmacological properties. In traditional medicine all over the world, plants which are rich in quinones are used for the treatment of a variety of diseases [16]. Various parts of *D.ensifolia* contain quinones,

such as:

- Armandinol (Dihydronaphtaquinone 2-hexyl-3-(2-hydroxyethyl)-2, 3-dihydronaphtaquinone 1-4), is isolated from the roots and leaves of *D. ensifolia* (Figure 4) [17].
- Chrysophanol or Chrysophanic acid (1, 8-dihydroxy-3-methylanthraquinone), is isolated from *Dianella longifolia*(Figure 4) [18].
- Isoeugenitol (Figure 4).
- 2,2'-binaphtho-1,4-quinone, dianellinone (Figure 3).
- triquinone, trianelinone (Figure 3) [19].
- Sty pandrone (Figure 3) [19].



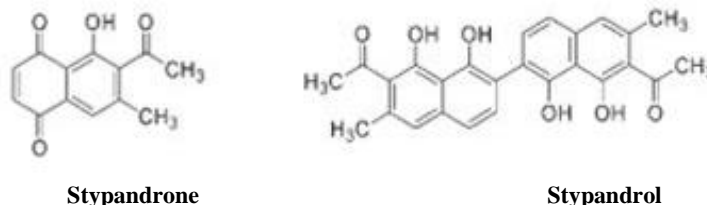


Fig 3: Dianellidin, Dianellinone, Trianellinone, Stypondrone and Stypondrol

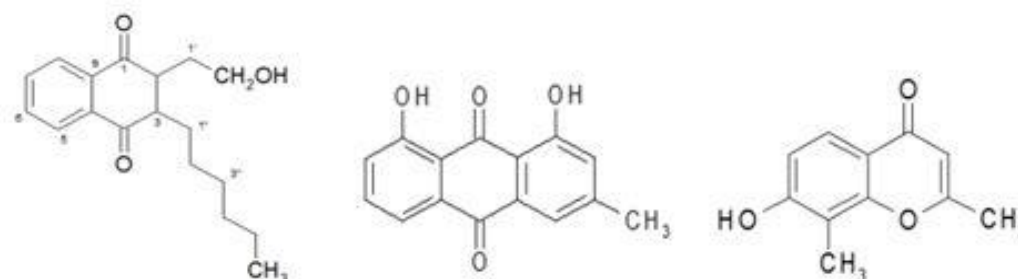


Fig 4: Quinones [17]

1. Armandinol, 2. Chrysophanol and 3. isoeugenitol

4.4 Chromones (natural pigment)

Chromone (or 1, 4-benzopyrone) is a derivative of benzopyran with a substituted keto group on the pyran ring. It is an isomer of coumarin. Derivatives of chromone are

collectively known as chromones. Most, though not all, chromones are also phenylpropanoids. Phytochemical investigation of the roots of *D. ensifolia* lead to the isolation of two chromones, namely Chromenes, benzo [b] pyran and Chromans, dihydrobenzo [b]-Pyran (Table1, Figure 5) [20-21].

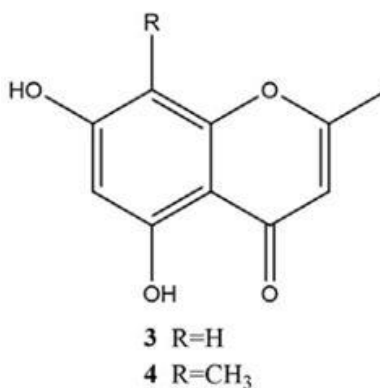


Fig 5: Chromones [20]

- (3). 5,7-dihydroxy-2-methylchromone
- (4). 5,7-dihydroxy-2,8-dimethylchromone

4.5 Glycosides

Four naphthalene glycosides, dianellin, 5-hydroxydianellin,

stellalderol and dianellose are reported (Figure 6). The derivatives of these naphthalenes have various biological activities, such as antioxidant, antimicrobial, anti-inflammatory, antiprotozoal, cytotoxic and anti-platelet aggregation [22].

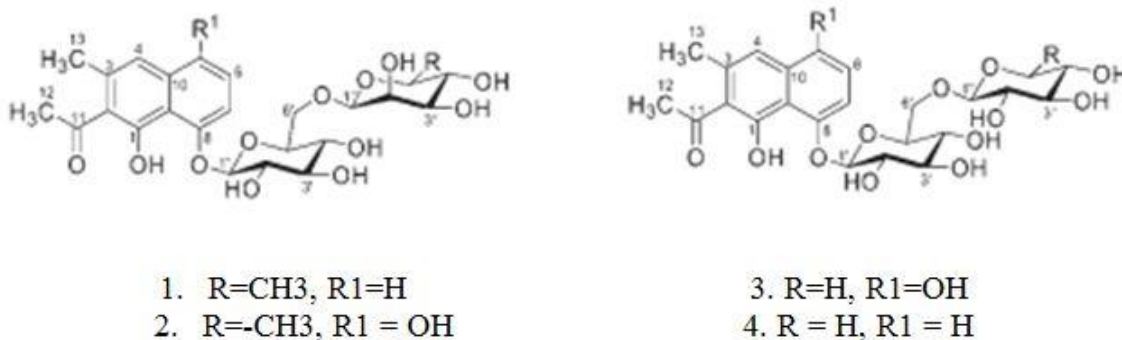


Fig 6: Glycosides of *Dianella ensifolia*

1. Dianellin, 2. 5-hydroxydianellin, 3. Stellalderol, 4. Dianellose

4.6 Water-soluble Carbohydrate

The water-soluble carbohydrates can be extracted from the underground parts of *Dianella nigra*. Extracts of *D. nigra* showed a more complex pattern of oligosaccharides. Linkage analysis showed that these extracts contained fructans with 1-linked Fruf, 6-linked Fruf and 1,6-branched Fruf, and 6-Glcp with only trace amounts of terminal Glcp [23].

4.7 Terpenoid

Three groups of terpenoids are known, essential oils,

cycloartane-type triterpenoids, and steroids (Figure 7). Recently, essential oils of the aerial parts of *D. ensifolia* is reported. The predominant essential oils are identified as alloromadendrene (7.3%), geranyl acetone (6.2%), hexahydro farnesyl acetone (4.4%), longifolene (4.2%) and β -caryophyllene (4.0%). (5) Cycloartane-type triterpenoids are isolated from the root of *D. ensifolia*, namely: 22-hydroxy-cycloaudenol, cycloneolitsol and cyclopholidonol. 22-hydroxy-cycloaudenol displayed cytotoxic effects against cancer cell lines B16-F10, A549 and MDA-MB-231 [24]. Two sterols are detected in the extract of aerial parts of *D. ensifolia*, stigmastenone and b-sitosterol [5,14].

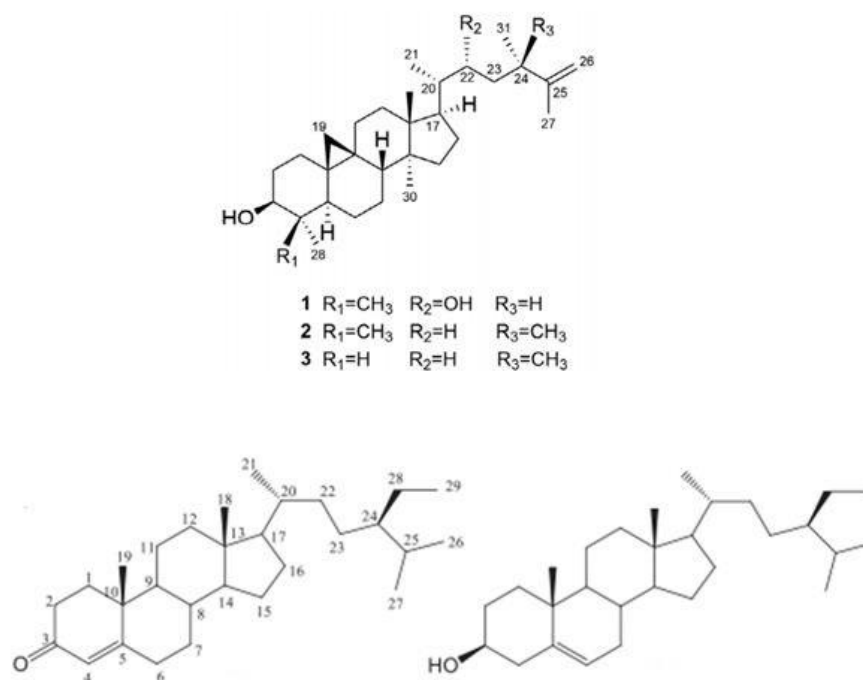


Fig 7: Cycloartane-type triterpenoid and steroids of *D.ensifolia*

Cycloartane-type triterpenoid: 22-hydroxy-cyclolaudenol (1), Steroids : Stigmastenone (4) and b-sitosterol (5)
Cycloneolitsol (2), Cyclopholidonol (3)

Table 1: Phytochemical constituents of *Dianella ensifolia*

Compounds	Part	Extraction method	Literature
Phenolics compounds			
1-(1,8-Dihydroxy-3-methyl-2-naphthalenyl) ethanone Dianellidin (syn. Musizin)	Root	Benzene, Chloroform	(11)
7-acetyl-4R,8-dihydroxy-6-methyl-1-tetralone methyl b-orsinol carboxylate	Aerial	macerated in Ethanol, dissolved in H ₂ O, successively extracted with n-hexane, CH ₂ Cl ₂ , Etil Acetate and n-butanol.	(14)
1,4-Naphthalenedione, 6-acetyl-5-hydroxy-7-methyl-6-Acetyl-5-hydroxy-7-methyl-1,4-naphthoquinone Stypandrone			
methyl 2,4-dihydroxy-3,5,6-trimethylbenzoate	Root	Benzene, Chloroform	(11)
methyl 2,4-dihydroxy-3,6-dimethylbenzoate	Root	Ethanol extract, suspended in H ₂ O, and extracted with petroleum ether, Chloroform and n-Butanol successively.	(20)
methyl orsellinate			
rhizinonic acid			
Hydro cinnamic acids, phenylpropanoids (C6-C3)			
Chromones			
5,7-dihydroxy-2-methylchromone	Root	Ethanol extract, suspended in H ₂ O and extracted with petroleum ether, Chloroform and n-Butanol successively.	(20)
5,7-dihydroxy-2,8-dimethylchromone		Benzene, Chloroform	(11)
5,7-dihydroxy-2,6,8-trimethylchromone	Root	Benzene, Chloroform	(11)
Acetophenones, phenylacetic acids (C6-C2)			
Acetophenone	Root	Benzene, Chloroform	(11)
2,4-dihydroxy-6-methoxy-3-methylacetophenone			
Flavonoids/Flavan C6-C3-C6			

2(S)-7,40-dimethoxy flavan	Aerial	macerated in Ethanol, dissolved in H ₂ O successively extracted with n-hexane, CH ₂ Cl ₂ , Etil Acetate and n-butanol.	(14)
2(S)-20,40-dihydroxy-7-methoxyflavan			
diaensi-biflavan (5-hydroxy-7,4'-dimethoxy (6,6''-methylene)-biflavan			
Amentoflavone			
5,7-dihydroxy-40-methoxyflavan			
(2S)-30,4'-dihydroxy7-methoxyflavan	Root	Ethanol extract, suspended in H ₂ O and extracted with petroleum ether, Chloroform and n-Butanol successively.	(20)
(2R)-7,4'-dihydroxy5-methoxy-8-methylflavan			
tupichinol A			
naringenin			
Farrerol			
Quinones			
Chrysophenol	Root	Benzene, Chloroform	(11)
Dianellinone			
Trianellinone			
Glycosides			
Dianellose	Aerial Root	Macerated in Ethanol 90%, dissolved in H ₂ O, successively extracted with n-hexane, CH ₂ Cl ₂ , Etil Acetate and n-butanol. Extracted with 3:1 Methanol/CH ₂ Cl ₂ , sequentially partitioned into CH ₂ Cl ₂ and Methanol	(14) (28)
Dianellin	Root	Benzene, Chloroform	(11)
5-hydroxydianellin	Root	Extracted with 3:1 Methanol/ CH ₂ Cl ₂ , sequentially partitioned (tritured) into CH ₂ Cl ₂ and Methanol	(28)
Stelladerol			
1. Terpenoid			
1.1. Essential oils			
Allo-aromadendrene (7.3%)	Aerial	Hydro distillation	(5)
Geranyl acetone (6.2%)			
Hexahydro farnesyl acetone (4.4%)			
Longifolene (4.2%)			
β-caryophyllene (4.0%).			
Cycloartane-type triterpenoid (Fig. 6.)			
22-hydroxy-cyclolaudenol	Root	Ethanol extract, suspended in water, then partitioned successively with petroleum ether, Chloroform and n-butanol.	(24)
Cycloneolitsol			
Cyclopholidonol			
Steroids (Fig.6)			
Stigmastenone	Aerial	macerated in Ethanol, dissolved in H ₂ O, successively extracted with n-hexane, CH ₂ Cl ₂ , Etil Acetate and n-butanol.	(14)
b-sitosterol			
2. Diarylpropane			
1-(2,4-dihydroxyphenyl)-3-(2,4-dimethoxy-3-methylphenyl) propane (DP or UP302)	Fruit	extracted with tetrahydrofuran, and the residue with a mixture of methanol-acetic acid-water	(25)
1-(2,4-dihydroxyphenyl)-3-(2,4-dimethoxy -3-methylphenyl) propane		Methanol extract	(12, 27)
Water soluble carbohydrates			
fructans with 1-linked Fruf, 6-linked Fruf and 1,6-branched Fruf.		Ethanol and water extracts	(23)
6-Glcp with only trace amounts of terminal Glcp.			

5. Pharmacology

5.1 Antioxidative activity

Phenolic compounds, essential oil and other chemicals in the various extracts of *D. ensifolia* are responsible for their anti oxidative activities such as 1-(2,4-dihydroxyphenyl)-3-(2,4-dimethoxy-3-methylphenyl) propane (DP or UP302), which is also a tyrosinase inhibitor [25, 26, 27]; various flavonoids, and essential oils (allo-aromadendrene, geranylactone, and β-caryophyllene) [5, 13].

2-hexyl-3-(2-hydroxyethyl)-2,3-dihydronaphtoquinone, chrysophanol and isoeugenitol have antioxidant activity based on the DPPH method at TLC, which is comparable with ascorbic acid and gallic acid [17]. Essential oils of *D. ensifolia* has antioxidant activity (DPPH, ABTS and FRAP) but it is weaker than BHT and Trolox. Its IC₅₀ are higher than IC₅₀ BHT and Trolox [5].

5.2 Antibacterial activities

The crude extract of the root of *D. ensifolia* displays significant antimicrobial activities. Dianellidin is reported for mild antimicrobial properties [28]. Essential oils of *D. ensifolia*

oil is a good bactericidal agent and effectively inhibit the growth of many studied bacteria strains. The good antibacterial activity of the *D. ensifolia* essential oil is may be associated with the presence of geranylactone, hexahydro farnesyl acetone, longifolene and β-caryophyllene. Hexahydro farnesyl acetone and geranyl lactone exhibit a potent antimicrobial and has a potential effect to inhibit the growth of Gram-positive bacteria [5].

5.3 Antivirus activities

The crude extract of the roots from *Dianella callicarpa* displays significant antiviral activities. Beside its mild antimicrobial properties, Dianellidin (2) shows also antiviral properties [28]. Extracts of various part of *D. ensifolia*, can be used in the traditional medicine for antiviral activity, such as poliovirus [29]. Chrysophanic acid (1,8-dihydroxy-3-methylantraquinone) can inhibit the replication of poliovirus types 2 and 3 (Picornaviridae) *in vitro*, and inhibit the early stage in the viral replication cycle, but does not have an irreversible virucidal effect on poliovirus particles. Chrysophanic acid does not have significant antiviral activity

against Coxsackievirus types A21 and B4, human rhinovirus type 2 (Picornaviridae), and the enveloped viruses Ross River virus (Togaviridae) and herpes simplex virus type 1 (Herpesviridae) [18].

5.4 Antitumor/anticancer properties

Several compounds showed antitumor or anticancer properties. Dianellin, stelladerol and dianellose display moderate antitumor activities [28]. A new cycloartane-type triterpenoid, named 22-hydroxy-cyclolaudenol, together with two known cycloartane-type triterpenoids can be isolated from the roots of *D. ensifolia*. Triterpenoid compound 22-hydroxy-cyclolaudenol displays cytotoxic effects against cancer cell lines B16-F10, A549 and MDA-MB-231 [24]. Alloaromadendrene inhibits significantly the cell growth and proliferation in the highly malignant + SA mammary epithelial cells, and possesses a potent *in vivo* protective effect against juglone-induced oxidative stress in the *Caenorhabditis elegans* and prolonged its lifespan.

5.5 Anti tyrosinase/Melanogenesis/hyperpigmentation

Extracts of *D. ensifolia* contain 1-(2,4-dihydroxyphenyl)-3-(2,4-dimethoxy-3-methylphenyl) propane (DP or UP302) that is an antioxidant and also a tyrosinase inhibitor [30]. Since, skin hyperpigmentation is linked to free radicals, therefore the free radical scavengers or antioxidants can slow that hyperpigmentation. The ability of DP antioxidant to increase the rate of fading [27]. DP is able to inhibit the melanin formation. The topical application of DP results in significant skin lightening and decrease of melanin production without effects on cell viability, melanocyte morphology or overall tissue histology. DP is a really potent tyrosinase inhibitor that suppresses melanin production in both cultured melanocytes and reconstructed skin with high potency and without adverse side effects [12].

5.6 Anthelmintic activity

Diospyrol has potential for anthelmintic activity (Figure 8) [31]. It is no progress since it is reported in 1986.

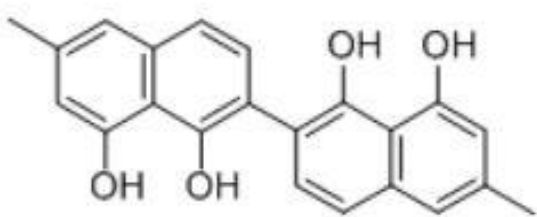


Fig 8: Diospyrol demonstrates an anthelmintic activity

5.7 Toxicity

Dianellidin, stypanrol and dianellinone are considered as toxic [31]. Stypanrol is neurotoxic [32]. Dianellidin (musizin) is importance in the formation of stypanrone and dianellinone. Both dianellidin and stypanrol are founded in the toxic specimens of *Stypantra imbricate* that is also a member of the Liliaceae and when ingested by liverstock can lead to a number of clinical and pathological effects culminating either in death or blindness [19].

6. Conclusion And Future Recommendations

6.1 Conclusions

From this study, three conclusions can be made:

- *D. ensifolia* is traditionally used as medicine for infectious and non-infectious diseases, but most of application is externally use. The application methods are infusion, cognation, and poultice.
- Most of the phytochemical constituents of *D. ensifolia* are investigated from the aerial part (leave) and roots, varied from polar, semi to nonpolar compounds. The information spread from phenolic compounds, flavonoid, water soluble carbohydrates, quinones, essential oil, steroids, diarylpropane, cycloartane-type triterpenoids, and chromones. No or limited reports are carried out with the use of LC MS/MS.
- Pharmacological studies show that *D. ensifolia* is good herbal medicine for wound healing because of its antibacterial activity, antiviral, antitumor and anti-inflammation, and anti melanogenesis.

6.2 Future recommendations

Today most of the synthetic drugs showed adverse and unacceptable side effects, however, impressive bioactivities with reduced toxicities are reported for many botanicals against several chronic or difficult-to-treat diseases.

- a) Ethnological exploration on the uses of *D. ensiformis* is still needed. Many grey literature available are not yet published in a standard journal.
- b) Further phytochemical investigations of all parts of *D. ensifolia* are needed to relate with its bioactivities. Bioactivity-based fractionation should be validated for accuracy, reproducibility, simplicity, and cost effectiveness.
- c) Pharmacological study of *D. ensifolia*
 - Antioxidative activities
 - Antibacterial, anti candida, antifungal (anti Tinea), anti Malassezia, antibiofilm, antiquorum sensing, and antiplasmid activities
 - Antiinflammation
 - Antiviral activities of *D. ensifolia* is valuable for the treatment of viral infections and can be used for the management of infections like herpes simplex virus (HSV), human immunodeficiency virus (HIV), influenza, etc [33]. Phytochemicals with antiviral potentials need to be studied in depth with standardization, chemical isolation, effectivity, molecular mechanism, along with *in vivo* toxicity and efficacy to reduce cost and time. The scientific approaches and methodologies used for the development of antiviral leads from traditional medicines against selected genetically and functionally diverse viral infections [34]
 - Clinical test for anti melanogenesis (anti tyrosinase, anti-hyperpigmentation)
 - Anthelmintic studies
 - Pharmacological study of the extract/external application as gel/cream, shampoo components, etc

Abbreviations

DPPH: 2,2-diphenyl-1-picrylhydrazyl

FRAP: Fluorescence recovery after photobleaching

BHT: Butylatedhydroxytoluene

ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)

TLC: Thin Layer Chromatography

GlcP: Glucopyranose

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None

Conflict of interest

The authors declare that there is no conflict of interest in writing this review.

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