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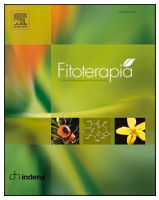

Review

An overview of the traditional use, phytochemistry, and biological activity of the genus *Homalanthus*

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ABSTRACT

Homalanthus species are native to tropical Asia and the Pacific region. This genus, comprising 23 accepted species, received less scientific attention compared to other genera of *the Euphorbiaceae* family. Seven *Homalanthus* species, such as *H. giganteus, H. macradenius, H. nutans, H. nervosus, N. novoguineensis, H. populneus,* and *H. populifolius,* have been reported to treat various health problems in traditional medicine. Only a few *Homalanthus* species have been investigated for their biological activities, including antibacterial, anti-HIV, anti-protozoal, estrogenic, and wound-healing activities. From a phytochemical point of view *ent*-atisane, *ent*-kaurane, and tigliane diterpenoids, triterpenoids, coumarins, and flavonol glycosides were found to be characteristic metabolites of the genus. The most promising compound is prostratin, isolated from *H. nutans*, with anti-HIV activity and the ability to eradicate the HIV reservoir in infected patients by mechanism of protein kinase C (PKC) agonist. This review provides information on traditional usage, phytochemistry, and biological activity of the genus *Homalanthus* with the aim to delineate future research directions.

1. Introduction

Medicinal plants have been used in the traditional medicinal system since ancient times to treat a wide range of diseases and to promote health [1]. Recording the medicinal relevance of species from high biodiversity areas is crucial because some of these plants' natural habitats are rapidly disappearing as a result of anthropogenic activities [2]. It is generally estimated that there are approximately between 250,000 and 500,000 species of higher plants. Approximately 10,000 of different plants around the world have recorded medicinal use, and >90% of present therapeutic classes derive from natural product prototype [3]. In the last decades, efforts have been extended to look beyond the limited number of plants with a history of traditional use as medicines and to comprehensively screen plant species, considering nature as an unending source of chemically diverse bioactive compounds for drug development [4–6].

Euphorbiaceae plant family, also known as the spurge family, is notably one of the most prominent flowering plant families with 227 accepted genera and over 8000 species [7]. *Euphorbiaceae* species are widely distributed, from Neotropical to Afrotropical, Indomalayan, Australasian, and Oceanian regions [8]. Species from this family exhibit a wide range of morphologies, including climbers, shrubs, and woody trees that often have latex in a variety of colors [9].

For decades, many regions of the world have traditionally used Euphorbiaceae species to treat various diseases such as fever, dysentery, skin problems (measles, ulcers, itches, and wound healing), gastric problems, urinary tract infections, malaria, and poisonous animal bites are among the possible usages. Although the latices from these plants are frequently described as an irritant, it was reported to be able to remove tumors and warts during the time of Hippocrates [10–15]. Many members of this family are economically important, including the rubber tree (*Hevea brasiliensis*), the candlenut (*Aleurites moluccana*), and tapioca (*Manihot esculenta*) [9].

One of the accepted genera that belong to Euphorbiaceae is *Homalanthus* (Table 1). Species from this genus have been used as medicinal plants to treat various diseases by many ethnicities throughout Southeast Asia and Oceania (Table 2). This genus was first reported in 1790 by Noronha as *Duania* and mentioned as *Omalanthus* in 1824 by Adrien jussieu. The *Omalanthus* was later revised to *Homalanthus* to match its Greek word meaning [7,16]. From 23 accepted species in this genus (Table 1), only a total of seven species have been studied for their phytochemistry and biological activity (Table 3 and Table 4). Perhaps

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Table 1
Accepted *Homalanthus* species and their native distribution [18].

Species	Date of discovery	Geographical distribution*
Homalanthus acuminatus (Müll. Arg.) Pax	1931	Society Islands
Homalanthus arfakiensis Hutch	1917	Maluku, New Guinea
Homalanthus caloneurus Airy Shaw	1968	Borneo
Homalanthus ebracteatua Guillaumin	1932	Vanuatu
Homalanthus fastuosus (Linden) Fern.–Vill.	1880	Philippines, Taiwan
Homalanthus giganteus Zoll. and Moritzi	1845	Jawa, Lesser Sunda Islands
Homalanthus grandifolius Ridl.	1917	Borneo, Sumatera
Homalanthus longipes Pax & K. Hoffm.	1912	Vanuatu
Homalanthus longistylus K. Schum and Lauterb.	1900	Bismarck Archipelago, New Guinea
Homalanthus macradenius Pax & K. Hoffm.	1912	Philippines
Homalanthus nervosus J.J. Sm.	1912	New Guinea
Homalanthus novoguineensis (Warb.) K. Schum.	1900	Bismarck Archipelago, Lesser Sunda Islands, Maluku, New Guinea, Northern Territory, Queensland, Solomon Islands, Western Australia
Homalanthus nutans (G. Frost) Guill.	1873	Caroline Islands, Cook Islands, Fiji, New Caledonia, Niue, Samoa, Society Islands, Tonga, Tubuai Islands, Vanuatu, Wallis and Futuna Islands
Homalanthus polyadenius Pax & K.Hoffm.	1919	New Guinea
Homalanthus polyandrus (Hook. F. ex Müll. Arg.) G. Nicholson	1885	Kermadec Islands
Homalanthus populifolius Graham	1827	Bismarck Archipelago, New Guinea, New South Wales, Norfolk Islands, Queensland, Solomon Islands, Victoria, North New Zealand
Homalanthus populneus (Geiseler) Pax	1892	Borneo, Jawa, Lesser Sunda Islands, Malaysia, Maluku, Philippines, Sulawesi, Sumatera, Thailand
Homalanthus remotus Esser	1997	New Guinea
Homalanthus repandus Schltr.	1906	New Caledonia
Homalanthus schlechteri Pax & K.Hoffm.	1912	New Caledonia
Homalanthus stillingifolius F. Muell.	1858	New South Wales, Queensland
Homalanthus stokesii F.Br.	1935	Tubuai Islands
Homalanthus trivalvis Airy Shaw	1968	Solomon Islands

* New Guinea refers to an island that crosses within Southeast Asia and Oceania region, while Papua New Guinea refers to a country in the Oceania region.

the most well-known species of this genus is *H. nutans,* which provides prostratin (**5**), a potential lead compound for HIV therapy [17]. The current data shows no published review on the genus *Homalanthus*. Therefore, this study aims to summarize the data from current literature on the traditional use, phytochemistry, and biological activity of the genus *Homalanthus*.

2. Methodology

A bibliographic search for this review was conducted by analyzing relevant databases. The searching was conducted in PubMed, ScienceDirect, Web of Knowledge, SciFinder, JSTOR, and Google Scholar using the search terms *"Homalanthus" and "Omalanthus"* associated with "Medicinal Plants" and "Phytochemicals." The literature in this review included theses, dissertations, and original research works in English

Table 2
Traditional uses of *Homalanthus* species.

Species	Part use	Traditional indication	ATC category*	Country origin	Ref
Homalanthus sp.	shoot	sore	D	Papua New Guinea	[22]
	stem	pancreatitis	M	Malaysia	[23]
H. giganteus	seeds	fever	N	Indonesia	[13]
H. macradenius	roots	spasm	M	Philippines	[24]
	leaves	wound healing	D	Philippines	[25]
	bark and leaves	toothache and blood vomiting	N A	Philippines	[26]
H. nutans	bark	purgative	A	Tonga	[27]
		tonic	A	Samoa	[28]
	leaves	facilitate birth	G	Vanuatu	[29]
		anti-inflammation	M	Samoa	[28]
	fruits	abortifacient	G	Vanuatu	[29]
	stem	yellow fever	J	Samoa	[28]
	roots	analgesic	N	Samoa	[28]
H. novoguineensis	na	respiratory disorder	R	Papua New Guinea	[30]
	succus	body ache	A	Papua New Guinea	[31]
	bark	heartburn	A	Papua New Guinea	[31]
	sap	topical ulcer	D	Papua New Guinea	[32]
H. nervosus	sap	boil and sore	D	Papua New Guinea	[33]
	leaves and flower	boil and sore	D	Papua New Guinea	[34]
H. populneus	roots	pregnancy and postpartum	G B	Indonesia	[35]
	leaves	rheumatism	M	Malaysia	[23]
H. populifolius	leaves	antimalarial	P	Indonesia	[36]
	leaves	leprous sore and motor disorder	D M	Indonesia	[37]

NA, not available/not mentioned; * ATC categories [38], A (alimentary tract and metabolism), B (blood and blood forming organs), C (cardiovascular systems), D (dermatological), G (genitourinary systems and sex hormones), H (systemic hormonal preparation), J (anti-infective for systemic use), L (antineoplastic and immunomodulating agent), M (musculoskeletal system), N (nervous system), P (antiparasitic, insecticide and repellents), R (respiratory systems), S (sensory organs), and V (various).

that were available until November 10, 2022. Information on traditional uses, chemical compounds, and pharmacological activities from each literature were extracted and grouped into an appropriate table. Plant names and distribution were confirmed using an online database from the World Flora Online (http://www.worldfloraonline.org/) and KEW Royal Botanic Garden (https://powo.science.kew.org/).

3. Botanical description and geographical distribution

The plants in the genus *Homalanthus are* usually trees or shrubs with smooth surface, and sometimes monoecious with milky latex. Leaves of this species are alternately arranged, long petiolate, sometimes with stipulate, peltate-shape leaves with entire to serrate margins and pinnate veins. The flower is usually bisexual with an inflorescence terminal and lobed fruit shape (2 or 3 lobes) with a thin crustaceous endocarp [18,19].

This genus primarily grows in wet and tropical regions, from Taiwan to Southeast Asia (Malaysia, Philippines, and Indonesia), Australia, and the Pacific (Table 1). Of the 23 species listed in this genus, seven are distributed in New Guinea (*H. arfakiensis, H. longistylus, H. nervosus, H. novoguineensis, H. polyadenius, H. populifolius* and *H. remotus*). Some

Table 3
Compounds isolated from *Homalanthus* species.

No	Class	Compounds	Part investigated	Source	Ref
1	diterpenoid	*ent*-3*S*-hydroxy-atis-16(17)-en-1,4-dione	stem	*H. acuminatus*	[44]
2	diterpenoid	*ent*-16*S*,17-dihydroxyatisane-3-one	stem	*H. acuminatus*	[44]
3	diterpenoid	*ent*-3*S*,16*S*,17-trihydroxykauran-2-one	stem	*H. acuminatus*	[44]
4	diterpenoid	*ent*-16*S*,17-dihydroxykauran-3-one	stem	*H. acuminatus*	[44]
5	diterpenoid	prostratin	stem	*H. nutans*	[17]
6	sterol	*β*-stigmasterol	leaves	*H. nervosus*	[16]
7	sterol	*β*-sitosterol	stem	*H. polyandrus*	[43]
8	triterpenoid	triterpene ketone ($C_{30}H_{48}O$)	stem	*H. polyandrus*	[43]
9	coumarin	scoparone	leaves	*H. nervosus*	[16]
10	flavonoid	hyperoside	leaves	*H. nervosus*	[16]
11	flavonoid	kaempferol 3-*O*-*β*-glucoside	leaves	*H. nervosus*	[16]

species are also endemic to certain islands, such as *H. polyandrous* on Kermadec Island, *H. caloneurus* on Borneo Island, and *H. stokesii* on Tubuai Island. Based on the International Union for Conservation Nature (IUCN), 12 out of 23 species have been assessed. Only the species *H. polyandrous* is threatened with extinction (categorized as vulnerable) [20].

4. Ethnomedicinal uses

Homalanthus species have been used widely in many traditional medicine systems, mainly in the Pacific. The information regarding the traditional use of *Homalanthus* is gathered from ethnobotanical survey reports. Ethnobotanical survey is usually used to study relationships of indigenous communities with plants. Such surveys are usually conducted through interviews with key informants to gather information on the plants used for rituals, foods, medicine, economic or other purposes [21]. From a drug discovery perspective, the most valuable information are that related to the utilization of plants for treatment different diseases, which provide the starting point searching new effective molecules from plants [6].

Seven species have been reported for their medicinal use, along with two ethnomedicinal reports with unspecified species. Table 2 outlines the various ethnomedicinal uses of *Homalanthus* species together with their used plant parts. The traditional indication for each species were then grouped based on their therapeutic classification according to the Anatomical Therapeutic Chemical (ATC) system, which the World Health Organization introduced.

According to the ATC classification, dermatological conditions account for 23% (6 of 26) of the ethnomedicinal use of *the genus Homalanthus*, followed by alimentary tract and musculoskeletal at 19% (5 of 26) (Table 2). The most cited species in the ethnomedicinal report is *H. nutans*. This plant is widely used by people in Tonga, Samoa, and Vanuatu as purgative, tonic, anti-inflammatory, antiviral, analgesic agent, and it is also used to ease the birth process. However, *H. nutans was* also reportedly used as an abortifacient [27–29]. *Homalanthus* species were also known for their other uses besides medicine; *H. nutans* and *H. populneus* were reported as a fish poison, and an ethnobotanical investigation in 1970 documented that certain *Homalanthus* species are being used for magic practice [22,39].

As for the part used, the most common are leaves at 32%, bark and stem at 24%, roots at 12%, and sap/latex at 8%. Seeds, shoots, flowers, fruits, and succus have a single occurrence. The use of leaves as the primary component in the ethnomedicinal study is not new; many studies have shown similar results. Traditional healers use leaves most probably because it is the most abundant plant part and it is easy to conserve and preserve [40–42].

5. Phytochemical constituent of the *Homalanthus* genus

The study of the chemical composition of the genus *Homalanthus* is relatively limited. To date, only 4 (*H. nutans, H. nervosus*, *H. acuminatus,* and *H. polyandrus*) of the 23 known species have been studied from the phytochemical point of view. Isolated compounds belong to the group of diterpenoids, triterpenoids, flavonoids, and coumarins [16,17,43,44]. The isolated compounds are summarized in Table 3.

5.1. Diterpenoids

Diterpenes occurring in plants of Euphorbiaceae can be characterized by a great structural diversity, resulting from various macrocyclic and polycyclic skeletons, and oxygen-containing functionalities. Specific compounds of the family Euphorbiaceae (and Thymelaeaceae) are the macrocyclic diterpenes, and their cyclization products are called “lower terpenes,” which have chemotaxonomic relevance (*e.g.*, casbane, jatrophane, ingenane, daphnane, tigliane, lathyrane, myrsinane, segetane, *etc.*) [45,46]. Other group of diterpene constituents of the family is the nonspecific “higher diterpenes”; their skeletons, like labdane, clerodane, abietane, atisane, kaurane, and bayerane, occur widely in different plant families outside of Euphorbiaceae. Diterpenoids are the focus of natural product drug discovery due to the variety of their therapeutically relevant biological activities (*e.g.*, antitumor, multidrug-resistance reversing, analgesic, and antiviral properties and anti-inflammatory activities) [47,48]. Some of these diterpenoids (*e.g.*, prostratin, resiniferatoxin, ingenol 3-angelate) serve as lead molecules for drug discovery.

Five diterpenoids have been isolated and identified from the species of *the genus Homalanthus* [17,44] (Table 3). Four diterpenes were isolated from the chloroform-soluble extract prepared from the stem wood of *H. acuminatus*. Among the isolated diterpenoids, compounds **1 and 2** were based on *ent*-atisane and **3** and **4** on *ent*-kaurane skeleton (Fig. 1) [44]. Stereochemistry of *ent*-3*S*-hydroxy-atis-16(17)-en-1,4-dione (**1**) was determined by X-ray crystallographic analysis. Multistep chromatographic separation of the chloroform-soluble fraction of fresh stem wood of *H. nutans* afforded the isolation of prostratin (12-deoxyphorbol 13-acetate) (**5**) that belongs to the tigliane skeletal type [17].

ent-3*S*-Hydroxy-atis-16(17)-en-1,4-dione (**1**) was reported from 5 Euphobiaceae species, *Euphorbia characias*, *E. guyoniana*, *E. fischeriana*, *E. neriifolia*, and *Stillingia sanguinolenta* [49–53]. It was tested for their inhibitory activity against breast cancer stem cells by the mammosphere formation assay in human breast cancer MCF-7 cells, and significant inhibitory activity was observed on mammosphere formation at a final concentration of 10 μM [51]. *ent*-16*S*,17-Dihydroxyatisane-3-one (**2**) was isolated from fifteen *Euphorbia*, one *Sapium* and one *Triadica* species [47,54]. Outside of Euphorbiaceae family it was reported from a *Solanum* species [55]. Wei et al. reported the acetylcholinesterase inhibitory activity of **2** with IC_{50} 77.38 ± 8.52 μM [56]. Further, its anti-HIV activity was also tested and IC_{50} value of 6.6 ± 3.2 μg/mL was measured [57]. *ent*-3*S*,16*s*,17-Trihydroxykauran-2-one (**3**) has the most limited occurrence, it was found to date only in *Euphorbia stracheyi*, *E. fischeriana*, and *E. yinshanica* [52,58,59]. Compound **4** occurs in different genera of Euphorbiaceae including *Euphorbia* (13), *Croton* (1), *Mallotus* (1), *Triadica* (1), *Sapium* (2), *Stillingia* (1) species. This compound was isolated from two genera (*Aloysia* and *Callicarpa*) of Verbenaceae species, too [60]. *ent*-16*S*,17-Dihydroxykauran-3-one (**4**) showed potentiating activity of nerve growth factor (NGF)-mediated neurite outgrowth from PC12 cells, with EC_{50} value of 19.7 μM, indicating its anti-neurodegenerative effect [61].

Prostratin (**5**) based on phorbol ester structure was first isolated and

Table 4
Biological activities from some *Homalanthus* species.

Activity	Species	Part investigated	Extract	Compound	Method	Effect	Ref
Antibacterial	*H. nutans*	leaves	80% ethanol	–	broth microdilution/*in vitro*	The ethanolic extract is effective against *P. aeruginosa* and clinical isolates *S. aureus* (SA3, SA8, SA9, SA10), with an MIC value of 4 μg/mL, which is comparable with the positive control.	[70]
	H. nervosus	leaves, stem bark, root bark	ethanol, then partitioned using petroleum ether, dichloromethane, and ethyl-acetate	–	bisk diffusion/*in vitro*	At a concentration of 4 mg/disk, extract and fraction showed broad-spectrum antibacterial properties. Furthermore, the ethyl-acetate fraction had better activities than chloramphenicol against *M. roseus, S. epidermidis, S. faecalis, K. pneumoniae*, and *S. marcescens.*	[71]
	H. nervosus	sap	petroleum ether dichloromethane methanol	–	bioautography/*in vitro*	No activity.	[84]
	H. novoguineensis	leaves and flower	petroleum ether dichloromethane methanol	–	bioautography/*in vitro*	No activity.	[84]
Anti-protozoal	*H. nervosus*	leaves, stem bark, root bark	ethanol, then partitioned using petroleum ether, dichloromethane, and ethyl acetate	–	disk diffusion/*in vitro*	Ethyl-acetate fraction (4 mg/disk) showed an inhibition zone of 16 mm against *Trichomonas vaginalis*, which is similar to chloramphenicol (10 μg/ disk).	[71]
Cytotoxic	*H. nutans*	leaves	80% ethanol	–	MTT assay/*in vitro*	The extract showed moderate cytotoxicity against human dermal adult fibroblast cell with an IC_{50} of 69.94 ± 2.08 μg/mL compared to reference drug fluorouracil, which had an IC value >128 μg/mL.	[70]
	H. nervosus	sap	petroleum ether dichloromethane methanol	–	brine shrimp lethality assay/*in vivo*	The petroleum ether and methanol extract have moderate toxicity with an LC_{50} of 44 μg/mL for both extract against *Artemisia salina*.	[84]
	H. novoguineensis	leaves and flower	petroleum ether dichloromethane methanol	–	brine shrimp lethality assay/*in vivo*	The methanol extract showed high toxicity against *Artemisia salina* with an LC_{50} value of 6 μg/mL.	[84]
Cell migration	*H. nutans*	leaves	80% ethanol	–	scratch assay/*in vitro*	At a concentration of 32 μg/mL, the ethanolic extract significantly stimulated cell migration after 24, 48, and 72 h.	[70]
Cell proliferation	*H. nutans*	leaves	80% ethanol	–	NHDF-FS cell assay/*in vitro*	The extract did not affect the proliferation of NHDF-FS cell at the tested concentration (32 μg/mL).	[70]
	H. populneus	leaves and bark	ethanol	–	MTT assay/*in vitro*	The ethanolic extracts from bark and leaves above 125 μg/mL significantly increase cell proliferation in peripheral blood mononuclear cell (PBMC).	[78]
Anti-HIV	*H. nutans*	stem	ethanol dichloromethane/ethanol (1:1)	**(6)**	cell assay/*in vitro*	Prostratin at noncytotoxic concentration (0.01–25 μM) showed protection activity of T-lymphoblastoid CEM-SS and C-8166 against HIV-1 virus.	[17]
	H. populneus	bark	ethanol	–	cell assay/*in vitro*	The extract at a range of 7.8–31.2 μg/mL had showed to downregulate CD4 and upregulate CD8. The extract also downregulates protein gp120 and gp41, which play a part on virus infiltration to the cell.	[78]
	H. nervosus	sap	methanol	–	cell assay/*in vitro*	The methanol extract had showed activities to inhibit PKC and PTK with the IC_{50} value of 10 and 42 μg/mL, respectively.	[84]
	H. novoguineensis	leaves and flower	methanol	–	cell assay/*in vitro*	The methanol extract inhibits PKC with IC_{50} at the value of 17 μg/mL.	[84]
	H. acuminatus	stem	ethanol dichloromethane/ethanol (1:1)	**(1)**	XTT-tetrazolium assay/*in vitro*	The compound showed a good anti-HIV activity with an IC_{50} value of 6 μg/mL.	[44]
	H. populneus	leaves and twig	methanol/dichloromethane (1:1)	–	PDBu binding assay/*in vitro*	At a concentration of 0.1 mg/mL, the extract had showed 93% displacement of ^{3}H-phorbol dibutyrate at binding site.	[85]
	H. acuminatus	stem	methanol/dichloromethane (1:1)	–	PDBu binding assay/*in vitro*	At a concentration of 0.1 mg/mL, the extract had showed 69% displacement of 'H-phorbol dibutyrate at binding site.	[85]
Estrogenic	*H. nutans*	fruit	na	–	animal model/*in vivo* uterus contraction/*in vitro*	The plant did not show any estrogenic activity in an animal model. The plant showed oxytocic activity *in vitro* using isolated uterus, beginning at a concentration of 2.5×10^{-3} g/mL.	[83]
Molluscicidal	*H. nervosus*	sap	petroleum ether dichloromethane methanol	–	animal model/*in vivo*	No activity.	[84]
	H. novoguineensis	leaves and flower	petroleum ether dichloromethane methanol	–	animal model/*in vivo*	No activity.	[84]

NA: not available/not mentioned.

identified from the poisonous plant *Pimelea prostrata* (Thymelaeaceae), native to New Zealand [62]. Later, it was identified in the Samoan medicinal plant *H. nutans* by using a bioassay-guided isolation process. In this experiment, XTT-tetrazolium assay was applied for anti-HIV-1 screening on the infected human lymphocyte cell lines which leads to the discovery of prostratin, the main anti-HIV compound of the plant [17]. The starting point of the study was the traditional knowledge of Samoan healers in Falealupo village who use the so called "mamala" tree to treat hepatitis. Prostratin (**5**) was later isolated from different *Euphorbia* species, *E. fischeriana* [63], *E. cornigera* [64], and *E. grandicornis* [65]. The stereochemistry of prostratin (**5**) was unambiguously determined by using an X-ray diffraction analysis [66].

The concentrations of prostratin (**5**) in *H. nutans* were investigated by a validated reversed-phase high-performance liquid chromatography (RP-HPLC) method. Four different populations from two Samoan islands were analyzed, and a significant variability of prostratin (**5**) content was observed. It was found that the stem tissue (ranging 0.2–52.6 μg/g) used by traditional healers contains a higher median concentration of prostratin (**5**) (3.5 μg/g) than root or leaf tissues (2.9 and 2.5 μg/g, respectively). The developed RP-HPLC method allows the selection of plants for agricultural cultivation aiming at the production of prostratin (**5**) for preclinical and clinical studies [67].

The first synthesis of prostratin was reported by Wender et al. in 2008. A semisynthesis was carried out starting from phorbol, which was readily available from renewable sources. This synthesis allowed the supply gram quantities of this therapeutically promising compound [68]. The chemical total synthesis of prostratin was elaborated by Tong et al. in 2018. The synthetic route includes 23 steps starting from cyclopentadiene [69].

5.2. Triterpenoids

Euphorbiaceae species usually are rich in triterpenes, especially the genus *Euphorbia*. Most of the triterpene that has been reported from *Euphorbiaceae* are oleanane, ursane, lupane, lanostane, friedelane, cycloartenol derivatives, and sterols [8]. The genus *Homalanthus* was barely investigated for triterpene constituents; only *β*-sitosterol (**6**) and an unidentified triterpene ketone with $C_{30}H_{48}O$ composition were isolated from the stem of *H. polyandrous* [43] and *β*-stigmasterol (**7**) from the leaves of *H. nervosus* [16] (Fig. 1).

5.3. Phenolic compounds

Currently, only one coumarin has been isolated from the genus *Homalanthus*. A simple coumarin, called scoparone **(9),** has been isolated and identified from the leaves of *H. nervosus* [16].

Nevertheless, only two flavonoid glucosides were reported from the genus *Homalanthus*. Hyperoside (**10**) and kaempferol-3-*O*-*β*-glucoside (**11**) were isolated from the methanolic and ethyl-acetate extracts from the leaves of *H. nervosus* (Fig. 1) [16]. Such flavonol glycosides are common compounds of Euphorbiaceae species [8].

6. Biological activities

Several biological assays have been carried out to support the ethnomedicinal claims of *Homalanthus* species. The biological assays conducted were *in vitro*, together with three *in vivo* assays focusing on *H. acuminatus, H. nervosus, H. nutans, H. novoguineensis,* and *H. populneus*. Among the *Homalanthus* species, *H. nutans* and *H. nervosus* are the most explored ones. Table 4 summarizes the biological activities of the genus.

6.1. Antibacterial and anti-protozoal activity

H. nutans and *H. nervosus* were tested for their *in vitro* antibacterial activity. The antibacterial effects of these species were mainly demonstrated in gram-positive bacteria. The ethanolic extract of the leaves of *H. nutans* was tested on bacterial pathogens associated with infected skin injuries, and this extract has been proven to inhibit the growth of *Pseudomonas aeruginosa* and clinical isolates of *Staphylococcus aureus* at a minimum inhibitory concentration (MIC) of 4 μg/mL [70]. In another study, ethanol extracts and their petroleum ether, dichloromethane, and ethyl-acetate fractions prepared from leaves, stem, and root barks of *H. nervosus* were tested against 13 gram-positive and 12 gram-negative bacteria and against the protozoa *Trichomonas vaginalis* by disk diffusion method [71]. The ethyl-acetate fraction of *H. nervosus* at 4 mg/disk had better activity than the positive control chloramphenicol against *Micrococcus roseus, Staphylococcus epidermidis, Streptococcus faecalis, Klebsiella pneumoniae*, and *Serratia marcescens.* The ethyl-acetate fraction of *H. nervosus* was found to have anti-protozoal activity against *Trichomonas vaginalis;* the activities of the leaf and root bark extracts were comparable to that of chloramphenicol [71].

The antibacterial activity from *H. nervosus* might be due to the existence of sterol and flavonoids. It was reported that stigmasterol (**6**) isolated from the stem bark of *Phyllanthus columnaris* shows antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) through modulation of genes that lead the interference of bacterial growth [72]. Stigmasterol was found to downregulate several genes that are involved in the biosynthesis of aminoacyl-tRNA (*lysA* and *thrS),* protein translation (*tsf* and *tuf*), RNA polymerase translation (*rpoA* and *rpoB*), and 43 genes that encoded the translation of ribosomal protein [72]. Hyperoside (**10**) and kaempferol 3-*O*-*β*-glucoside (**11**) can also contribute to the antibacterial activity by directly damaging the bacterial membrane [73]. However, antimicrobial mechanism of action of other compounds has not yet been elucidated.

6.2. Antiviral and HIV anti-latency activities

The antiviral activity of prostratin (**5**) was discovered in an experiment performed on *H. nutans*, although this compound was first isolated from *Pimelea prostrata* (strathmore weed), a small endemic shrub from New Zealand [17,62]. The leaves of *H. nutans* in the form of water infusions have been used by the Samoan healers to treat back pain, abdominal swelling, and circumcision wounds, while the root infusion was used to suppress diarrhea and as an analgesic, and stem woods were prepared to treat yellow fever (Table 2). Starting from the traditional medicine knowledge, the extracts of *H. nutans* was investigated *in vitro* for antiviral activity by tetrazolium-based assay, and the inhibition of cytopathic effects of human immunodeficiency virus (HIV-1) was detected. Prostratin (**5**) was isolated from the active extract by using a bioassay to monitor the HIV-1 cytopathic effect. This compound was found to be capable of preventing the reproduction of HIV-1 in lymphocytic and monocytoid target cells at noncytotoxic concentrations (from 20.1 to >25 μM) and completely protecting susceptible cells from the lytic effects of HIV-1. Its cytoprotective concentration was ≥11 μM that essentially stopped virus reproduction in the studied cell lines [17].

Furthermore, it was interesting to test if prostratin (**5**) as a phorbol derivative is able to bind to protein kinase C (PKC) and either activate or inhibit it. *In vitro* experiments have showed that prostratin (**5**) binds to and activates protein kinase C in CEM-SS cells and causes additional biochemical reactions in C3H10T1/2 cells that are typical of phorbol esters [17]. Prostratin (**5**) is also capable of inhibiting *de novo* HIV infection most likely as it induces the downregulation of HIV receptors from the surface of target cells. This compound blocks HIV infection by downregulating the HIV cellular entry receptors CD4 and CXCR4 [74]. Prostratin (**5**) shares structural similarities with phorbol esters, which are known to promote tumor growth, but it was found to have no tumor-promoting properties [17].

Prostratin (**5**) was reported to be able to upregulate viral expression from latent provirus. Latently infected cells serve as a constant source of viral reactivation; hence, this discovery was significant. The persistence of latently infected cellular reservoirs constitutes the principal obstacle

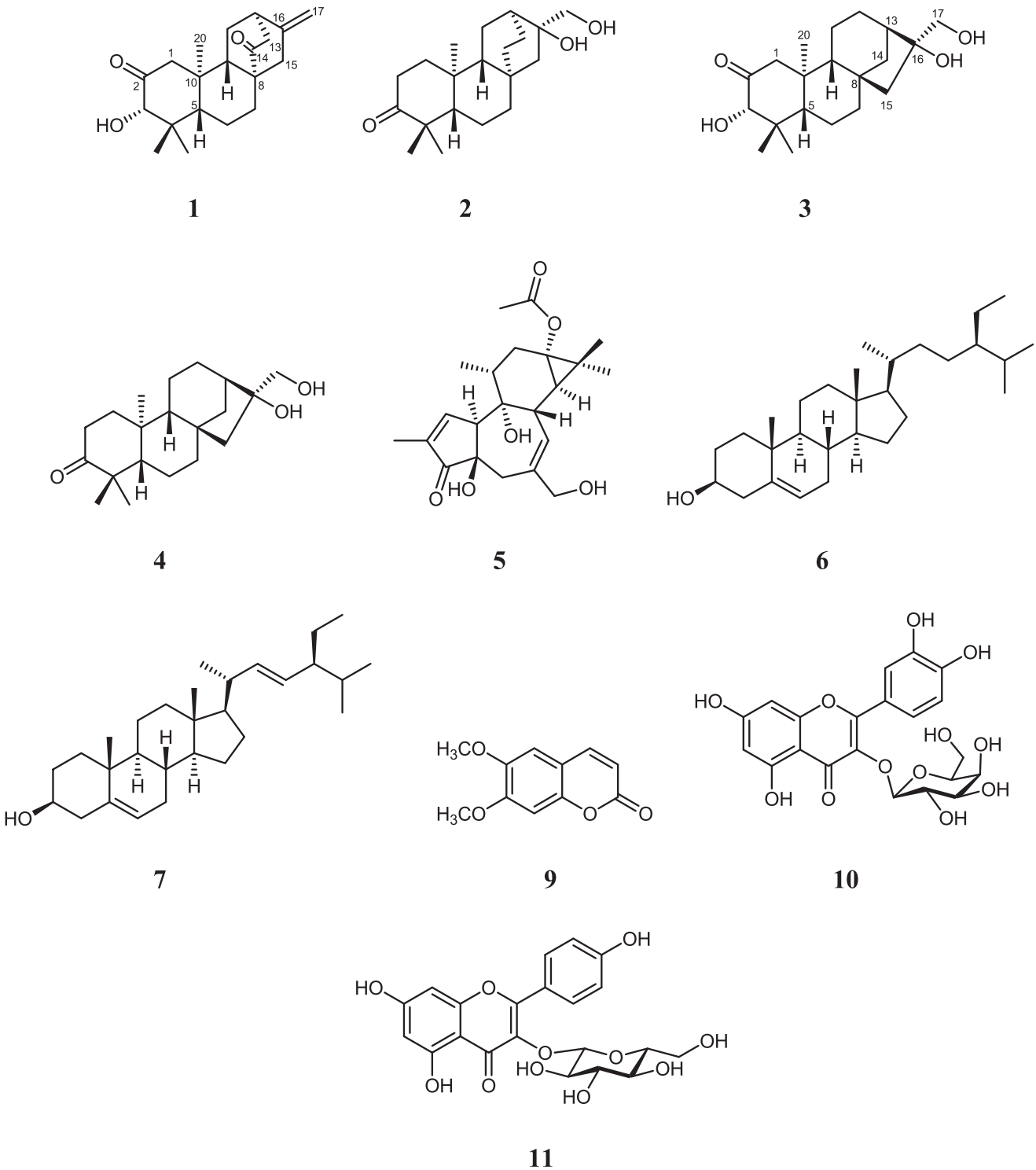

Fig. 1. Compounds isolated from *Homalanthus* species.

to virus eradication with highly active anti-retroviral therapy. It was demonstrated that prostratin (**5**) effectively activate HIV-1 gene expression in the latently infected cells and activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and c-Jun N-terminal kinase and extracellular signal-regulated kinase pathways [75,76].

It was found by Brown et al. in 2005 that prostratin (**5**) induces the immediate–early, early, and late gene expression of Kaposi's sarcoma-associated herpesvirus (KSHV) in two lymphoma cell lines *in vitro* [77].

The extract of the tropical rainforest tree *H. acuminatus* was found to be active in the NCI AIDS-antiviral screen. A diterpene isolated from the extract, *ent*-3*S*-hydroxy-atis-16(17)-en-1,4-dione (**1**) was effective in the anti-HIV screen made by XTT-tetrazolium assay. It showed a maximum of 50% protection to HIV-infected cells at a concentration of 6 μg/mL, and it was noncytotoxic to uninfected control cells. However, in a higher concentration (12 μg/mL), cytotoxic effects increased in both control and HIV-infected cells; therefore this compound was not selected for further development [44].

A study by Sintya et al. aimed to analyze the effect of the extract of *H. populneus* on the expression of CD4 and CD8, both of which are

critical components of the body's HIV defense system. The expressions of Gp41 and Gp120 were analyzed by using talicytometry and an enzyme-linked immunosorbent assay, respectively, to examine the impact of the extract on HIV-1. It was revealed that the extract of *H. populneus* decreased the expression of CD4 receptor in both T-lymphoblast cell line and peripheral blood mononuclear cell (PBMC) (CEM). On the other hand, this extract increased the expression of PBMC CD8, and it was able to lower the proportion of the proteins gp41 and gp120 in CEM cultures [78].

6.3. Other biological activities

As part of a study, the wound-healing properties of plants used in traditional Samoan medicine, including *H. nutans* (mentioned as *Omalanthus*), was investigated *in vitro* by Frankova et al. on the proliferation and migration of human dermal fibroblasts. It was demonstrated that *H. nutans* extract significantly stimulates cell migration to the wound area [70]. The wound-healing mechanism is closely related to the activation of NF-κB. The activation of NF-κB will trigger the release of pro-inflammatory cytokines, including IL-10 and IL-13, that stimulate tissue repair [79]. Prostratin (**5**) has been reported to stimulate IKK-dependent phosphorylation leading to the activation of NF-κB [80]. A fascinating *in vivo* experiment investigating the regeneration of *Xenopus laevis* tadpole tail was done by Bishop et al. A significant percentage of amputated tadpoles were able to regenerate after 30 min of incubation in 10 μM of prostratin compared to vehicle control [81].

The only compound isolated from *H. nutans* was prostratin (**5**). However, its mechanism on cell migration has not yet been reported. Nevertheless, another tigliane diterpene (12-tigloyl-13-(2-methyl-butanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliane-3-one) was reported to possess the ability to enhance keratinocyte migration and wound repopulation *via* PKC activation [82].

Bourdy et al. studied five plant species that were used in the traditional medicine of Vanuatu (Melanesia) for the purposes relating to human reproduction. *H. nutans* was involved in this study because its fruits were applied traditionally as abortifacients. The infusions of the plant materials were assayed for estrogenic effects *in vivo* and oxytocic activities on isolated rat uterus *in vitro*. The extract of *H. nutans* prepared from fresh plant exhibited no estrogenic activity, but it was effective in the oxytocic test at a concentration of 2.5×10^{-3} g/mL [83]. This study of oxytocic activity confirmed the ethnobotanical use of the plant as a powerful abortifacient. However, the compounds responsible for this activity were not identified yet.

In the study by Nick et al., medicinal plants used in the traditional medicine of Papua New Guinea were analyzed for bioactivities. Seventeen species were tested, including *H. nervosus* and *H. novoguineensis*, for PKC and tyrosine-specific protein kinase (PTK) of epidermal growth factor receptor activities *in vitro*. The methanolic extract of *H. nervosus* and *H. novoguineensis* were demonstrated to have high PKC inhibitory activities with IC_{50} values of 10 and 17 μg/mL, respectively. The predominance of activity in the methanolic extracts could be due to the presence of ubiquitous, hydroxylated flavones, known as inhibitors of protein kinases. Accordingly, in this assay, the dichloromethane and petroleum ether extracts, which do not contain such compounds, were inactive. The methanolic extract of *H. nervosus* moderately inhibited PTK; 42% inhibition was shown at a concentration of 50 μg/mL [84]. Molluscicidal activities of *H. nervosus* and *H. novoguineensis* extracts were also tested, but both were inactive in this assay [84].

6.4. Toxicity

Three species (*H. nutans, H. nervosus,* and *H. novoguineensis*) have been reported for their moderate to high toxic activities. The methanol extracts from the leaves and flower of *H. novoguineensis* have been reported to be highly toxic against *Artemia salina* (LC_{50} 6 μg/mL). Highly toxic properties of the methanolic and petroleum ether extracts of *H. nervosus* sap (LC_{50} 44 μg/mL for both) in the brine shrimp test were observed [84]. The methanolic extract from the leaves of *H. nutans* had demonstrated moderate cytotoxicity against human dermal adult fibroblast cells with an IC_{50} value of 69.94 ± 2.08 μg/mL [70].

7. Conclusion and future perspective

This review highlights the knowledge about the traditional use, phytochemistry, and biological activities of *Homalanthus* species. The plants from this genus are mostly distributed in the Indomalayan, Australasian, and Oceanian region. According to some field investigation reports, species from the genus *Homalanthus* have been used traditionally to treat various ailments, including fever, skin disorders, malaria, toothache, heartburn, inflammation, respiratory disease, rheumatism, and many others. Some *in vivo* and *in vitro* pharmacological testings confirm the traditional use of the species of this genus. For instance, the stem of *H. nutans* is traditionally used to treat yellow fever, and prostratin (**5**) isolated from it has antiviral activity. Prostratin (**5**) has been shown to be a high potential as an adjuvant therapy for the treatment of latent HIV infection.

Despite the success story of finding the anti-HIV agent prostratin (**5**), the research of the genus *Homalanthus* seems did not highly escalate. Up to date, only 5 (21.7%) out of 23 accepted species of this genus are being investigated for their biological activities, and only four species (17.4%) are subjected to further phytochemical isolation. Diterpenoids, triterpenoids, flavonoids, and coumarins are listed as the secondary metabolites isolated from this genus. Currently, scientific literature on this genus remains scarce, thus leaving us with many opportunities to explore. Therefore, multidisciplinary studies are required to fully explore their potential in the search of promising compounds for drug discovery.

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Dyke Gita Wirasisya: Conceptualization, Investigation, Data curation, Writing – original draft. **Judit Hohmann:** Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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