



The medicinal potential of plants from the *Adenostemma* genus

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ABSTRACT

Adenostemma is a genus in the Asteraceae family consisting of more than 20 species distributed in tropical regions of Asia, Africa, Australia, America, and the Pacific Islands. They have been used in folk medicine as remedies for diseases such as fever, inflammation, edema, digestive disorders, and lung injury. This review aims to provide information about *Adenostemma* species, the traditional uses of these species, chemical constituents, and therapeutic potential based on scientific evidence. The literature search was conducted through Google Scholar, PubMed, ScienceDirect, and KNApSAcK using several search terms. It was revealed in our studies that *Adenostemma* plants have various secondary metabolites, including alkaloids, terpenoids, phenolics, flavonoids, fatty acids, saponins, and tannins. Antioxidant, anti-inflammatory, antimelanogenic, antitumor, and antiviral activities have been shown by scientific evidence of its extracts and isolated compounds. *Adenostemma* species were demonstrated by this investigation to offer a prospective source for the development of new drugs. However, phytochemical and pharmacological data are currently limited and require further studies.

INTRODUCTION

Adenostemma plants are members of the Asteraceae family. These plants are annual or perennial herbs that grow wild, commonly known as sticky daisies. They are widely distributed in tropical regions of Asia, Africa, and America (Koyama, 2002). *Adenostemma* is frequently reported to have 20–24 species, according to King and Robinson (1974), Porteners (1992), and Bremer *et al.* (1994). However, Koyama (2002) claimed that there might be more than 30 species of *Adenostemma* J. R. et G. Forst (tribe Eupatorieae) that have been identified and may be found in Asia, Africa, Australia, America, and several oceanic islands.

Common names in Southeast Asia were rumput tahi babi, sumbong gajah, rumput pasir (Malay), daun tempel daging boton (Filipino), and tuyenhung (Vietnamese) (Wiert, 2006).

Most *Adenostemma* species are small, with erect and branched stems, opposite leaves, and terminal inflorescences with many flowered heads. Their leaves and whole plants have been used in folk medicine to remedy diseases such as fever, inflammation, and lung injury. Numerous studies have been conducted on the chemical composition and bioactivity of Asteraceae plants. Nevertheless, plants in the genus *Adenostemma* are still generally unknown. Since their purported therapeutic properties have been confirmed by scientific studies, interest in these plants has grown recently. However, no comprehensive review has summarized the medicinal applications, phytochemical characteristics, and pharmacological properties of the species in the genus. Therefore, we thoroughly discuss the subjects and evaluate the scientific data supporting the therapeutic use of *Adenostemma* in this study.

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METHODS

We searched the literature through Google Scholar (<https://scholar.google.com/>), PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), ScienceDirect (<https://www.sciencedirect.com/>), and KNApSACk (<http://www.knapsackfamily.com/KNApSACk/>). We used articles published between 1935 and 2022 due to the scarcity of information on *Adenostemma*. The search terms used to access the database were “*Adenostemma*,” “Chemical Compound of *Adenostemma*,” and “Bioactivities of *Adenostemma*.” We carefully studied all the obtained literature, and 70 publications were chosen for this review.

RESULTS AND DISCUSSION

Species, distributions, and traditional uses

Adenostemma species, their distribution, and their traditional uses are shown in Table 1. In this article, we describe 10 species of *Adenostemma* found worldwide, with various local names and traditional uses that have been previously reported.

Adenostemma lavenia (L.) O. Kuntze is the most widely reported species in the genus *Adenostemma*. *Adenostemma lavenia* has different local names in different world regions. *Adenostemma lavenia* (L.) O. Kuntze was recognized by Backer and Bakhuizen van den Brink (1965), who successfully identified *Adenostemma* in Java, Indonesia. They described *A. lavenia* as having a glandular-hairy or subglabrous stem, ovate, obtuse, acute apex, dentate, or serrate leaves, and achenes at maturity were densely muricate. Individuals in this species thrive in humid environments, areas with some shade, woodlands, brushwood, ditches, and by the side of the road. Additionally, Tjitrosoedirdjo (2002) identified *A. lavenia* in Sumatera, Indonesia. The morphological traits were comparable to and relatively consistent with those described by Backer and Bakhuizen van den Brink (1965).

A survey of medicinal plants in North Kalimantan, Indonesia, conducted by Arthur in 1952, found that *A. lavenia* leaf extract (local name: tomali mali or nonokot) was traditionally used by local people to treat fever and healing after childbirth (Arthur, 2011). The root of this plant is chewed with an areca nut, and its ginger is used as a cough remedy. The crushed leaves can be used to soothe sunburned skin, and the leaves withered over a fire can be used to ripen boils. The leaves can also prevent hair loss by washing the hair with them. Leaves mixed with salt can be used for sore throats (Batubara and Prastya, 2020; Kusumawati *et al.*, 2003).

Adenostemma lavenia may also be found in Southeast Asian regions, such as Thailand (Koyama *et al.*, 2016). However, an *A. lavenia* with eight varieties was recognized in India and South Asia (Panigrahi, 1975). Mathew and Mathew (1983) identified another species besides *A. lavenia* in south India, i.e., *Adenostemma viscosum*. The whole plant of *A. lavenia* is used against digestive disorders in the Wayanad district of Kerala, India (Prasad *et al.*, 2013). *Adenostemma lavenia* is also widely distributed in tropical regions of East Asia, such as Japan, Korea, the Taiwan region, and mainland China. *Adenostemma lavenia* has long been used as an herbal medicine for treating inflammation, edema, pneumonia, and lung congestion in the Taiwan region (Cheng *et al.*, 1979). Leaf or whole plant is usually used by the Red-headed Yao people in Jinping from Yunan Province, China,

to treat flu, toothache, falls-related injuries, hepatitis, pneumonia, quinsy, enteritis, lymphadenitis, stomach bug, stomach calculus, and vesical calculus (Long and Li, 2004). Meanwhile, *A. lavenia* has two varieties in Australia: var. *lavenia* and var. *lanceolatum* (Miq.) Koster (Orchard, 2011).

Adenostemma madurense DC, a new species from south India, was published by Panigrahi (1975). However, based on the morphological characteristics of the leaf, peduncle, and achene, Panigrahi (1975) regarded this taxon as a variety of *A. lavenia*. Koyama (2001) highlighted that *A. madurense* has broadly ovate leaves, an obtuse leaf margin, and slightly glandular muricate in the upper part of the achene, recognizing it as a separate species. Furthermore, Jeong *et al.* (2017) reported new distribution records of *A. madurense* on Jeju Island in Korea. They described that *A. madurense* is distinguished from *A. lavenia* by its broad ovate or ovate to oblong leaves, about 15–21 cm long by 7–12 cm wide, and smooth achenes with a small muricate on the upper surface, growing on dry mountain slopes in evergreen forests, while *A. lavenia* is found in wetland areas and on the edge of ponds. *Adenostemma madurense* is primarily distributed in Nepal, Thailand, Japan, and the Taiwan region.

Adenostemma platyphyllum Cass has erect, up to 100 cm tall, petioles up to 8 cm, opposite, broadly ovate up to 18 cm long, and up to 13 cm wide, rough-surfaced leaves, white flowers, and somewhat purple leaves (Blair and Madrigal, 2005; Nurlela *et al.*, 2022b). King *et al.* (1976) also reported that *A. platyphyllum* had a chromosome number (*n*) equal to five. In Ecuador (South America), *A. platyphyllum* was used as an antitussive, analgesic, and remedy for snake bites and scorpion stings. The three *Adenostemma* plant species described so far, *A. lavenia*, *A. madurense*, and *A. platyphyllum*, are displayed in Figure 1. They were collected from the Biopharmaca Conservation and Cultivation Station, Tropical Biopharmaca Research Center, IPB University, Bogor, and were identified by the curator of herbarium Bandungense (FIPIA) SITH ITB.

Adenostemma macrophyllum is a large herb 0.3–1 m tall, bears large broadly ovate leaves and adult achenes black and smooth. It may be found mainly throughout Java and Sumatera in Indonesia, Sabah in peninsular Malaysia, and eastern Queensland in Australia (Backer and Bakhuizen van den Brink, 1965; Orchard, 2011; Tjitrosoedirdjo, 2002).

Adenostemma parviflorum was recognized as a distinct taxon (Koster, 1935; Koyama, 2002; Panigrahi, 1975) but was identified as *A. lavenia* var. *parviflorum* by Backer and Bakhuizen van den Brink (1965) and Koster (1966). *Adenostemma parviflorum* differs from other species mainly in its smaller florets and heights between 0.35 and 0.7 m. Its habitats are secondary forests, bushes near rivers, grasslands, and swampy areas, in areas with an altitude of 500–2,000 m. *Adenostemma parviflorum* is distributed in Thailand, China, the Pacific Islands, Hawaii, Malesia, Sumatra, Java, Kalimantan, Sulawesi, Panay, and New Guinea (Tjitrosoedirdjo, 2002).

Adenostemma viscosum is distinct from *A. lavenia*, being found from Africa to Sri Lanka, India, Indonesia, and the Pacific as far as Hawai'i, while *A. lavenia* is restricted to its type of site in Sri Lanka (King *et al.*, 1976). *Adenostemma viscosum* is widespread in East Africa, such as in the Republic of Kenya,

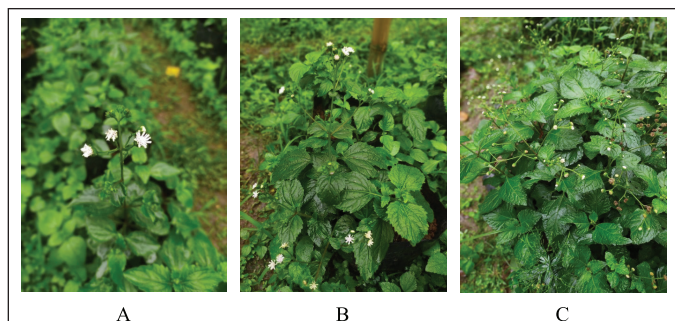
Table 1. List of *Adenostemma* species, distributions, and traditional uses.

Plant species	Distribution area	Local name	Traditional use	References
<i>A. lavenia</i> O. Kuntze	North Borneo/ Kalimantan (Indonesia)	Tomali mali, nonokot	The leaves extract for healing purposes after childbirth	Arthur, 2011
	China	Fa ha mi	The leaves or whole plant are made into a poultice to treat flu, toothache, injuries from falls, pneumonia, hepatitis, enteritis, and stomach pain	Long and Li, 2004
	Australia	-	-	Orchard, 2011
	Thailand	-	-	Koyama, 2002
	Indonesia	Legetan warak, udu tai, rumput babi	The leaves are used to treat sore throat, skin diseases, dysentery, headaches, toothaches, infections, and inflammations	Rahminiwati <i>et al.</i> , 2022
	Kerala (India)	Karimpatta	The ground of a whole plant mixed with water to treat ulcers	Prasad, 2013
	The Taiwan region	-	The whole plant cured inflammation, lung congestion, pneumonia, and edema	Cheng <i>et al.</i> , 1979
<i>A. madurense</i> DC	Vietnam	Cúc dĩnh	Medicinal plant	Huyen <i>et al.</i> , 2019
	Korea	-	-	Jeong <i>et al.</i> , 2017
	Japan	-	-	Maeda <i>et al.</i> , 2022
	Thailand	-	-	Koyama, 2002
<i>A. platyphyllum</i> Cass	Indonesia	-	Antimicrobial, antioxidant, and anti-inflammation agent	Fauzan <i>et al.</i> , 2018
	Ecuador	Mama juana	Antitussive, analgesic, snake bites, and scorpion stings	King <i>et al.</i> 1976; Moncayo <i>et al.</i> , 2021
<i>Adenostemma macrophyllum</i>	Indonesia	-	-	Backer and Bakhuizen van den Brink, 1965; Tjitrosoedirdjo, 2002
	Australia, Malaysia	-	-	Orchard, 2011
<i>A. parviflorum</i>	Thailand	-	-	Koyama, 2002
	Indonesia	-	-	Tjitrosoedirdjo, 2002
<i>A. viscosum</i>	Republic of Kenya; Republic of Uganda; Republic of Rwanda; United Republic of Tanzania; Republic of Malawi; Republic of Burundi; Republic of Zambia	-	-	Kokwaro 2009
	Malaysia	Bulak manok	The leaves and stem are used to treat headaches and sinusitis, the leaf extract prevents infections after childbirth, and the root decoction treats stomachaches	Larsen 1999; Girardi <i>et al.</i> , 2015; Abuga <i>et al.</i> , 2022
	Vietnam	Cò hôi hoa trắng	Edible and medicinal plant	Girardi <i>et al.</i> , 2015
<i>A. brasilianum</i>	Marquesas islands, French Polynesia, Pacific Ocean	Vaianu/tahatahavai	Headache, vertigo, sinusitis, migraine	Girardi <i>et al.</i> , 2015
	Argentina and Brazil	-	-	King and Robinson, 1987; Moraes and Monteiro, 2006
<i>Adenostemma caffra/caffrum</i>	Republic of Uganda	-	The plant part (usually leaves) is crushed and packed into or onto the skin's surface over a wound Leaves macerated water used to treat sore throat	Hamill <i>et al.</i> , 2000; Kalema and Ssegawa, 2007
	Nigeria	-	-	Omoigui, 2015

Continued

Table 1. List of *Adenostemma* species, distributions, and traditional uses.

Plant species	Distribution area	Local name	Traditional use	References
<i>Adenostemma perrottetii</i>	Federal democratic Republic of Ethiopia	bo-charo, shoj-charo	The stems and leaves used for curing dysentery and snakebite	Giday <i>et al.</i> , 2010
	Federal Republic of Nigeria	Ifuk ikot	Powdered and macerated leaves in water as an infusion to cure measles and chicken fox	Ajibesin <i>et al.</i> 2008
<i>Adenostemma mauritanium</i>	Nigeria	-	-	Omoigui, 2015
	Uganda	Omuhurambwa/ Cureera	Infusion drunk to treat Kwashiorkor	Gumisiriza <i>et al.</i> , 2021

**Figure 1.** (A) *Adenostemma lavenia*. (B) *Adenostemma madurense*. (C) *Adenostemma platyphyllum*.

the Republic of Uganda, the Republic of Rwanda, the United Republic of Tanzania, the Republic of Malawi, the Republic of Burundi, and the Republic of Zambia (Kokwaro, 2009). In Sabah, Malaysia, the leaf extract of *A. viscosum* was used to prevent postpartum infections. At the same time, root decoction is used to treat stomachaches in the Malaysian Peninsula. The stems and leaves of *A. viscosum* may also be used to cure migraines, sinusitis, vertigo, and headaches (Abuga *et al.*, 2022).

Another *Adenostemma* species distributed in the south American region—Argentina and Brazil—is *Adenostemma brasilianum*. This species lives in low-elevation areas, in the understory of forests or along their borders, in damp, and in partially shaded environments (King and Robinson, 1987; Moraes and Monteiro, 2006).

Adenostemma is a medicinal plant used to control ailments afflicting humans for a long time in Africa (Retief, 2002). For example, in the Kabale district of Uganda, in East Africa, the leaves of *Adenostemma caffra* DC or *Adenostemma caffrum* DC were used to cure sore throats and skin wounds (Hamill *et al.*, 2000). In other East African regions, such as Ethiopia, the stem and leaf of *Adenostemma perrottetii* DC. are used to treat dysentery and snakebite via the oral route (Giday *et al.*, 2010). *Adenostemma mauritanium* was also used to cure coughs, measles, and chicken pox by making powdered leaves and macerating them in water as an infusion in Nigeria (Ajibesin *et al.*, 2008).

Chemical compounds

Arthur (2011) conducted an earlier study of the chemical composition of the genus *Adenostemma* in Borneo, Indonesia. A predominance of alkaloids and essential oils was revealed in this study on leaves and the whole plant of *A. lavenia* by qualitative phytochemical assays. Due to their traditional use being widespread

in some regions of the world, *A. lavenia* is the most studied species for its chemical contents and bioactivities. We summarized the chemical components available in *Adenostemma* in Table 2.

The chemical constituents in *Adenostemma* tissues and extracts have been identified and precisely quantified using different methods. In our previous study, we used the spectrophotometry method to quantify the total phenolic content (TPC) and total flavonoid content (TFC) of three species of *Adenostemma*. The water extract of *A. lavenia* leaves was reported by that study to possess higher TPC (14.40 mg GAE/g DW) and TFC (4.73 mg QE/g DW) than *A. madurense* and *A. platyphyllum* (Nurlela *et al.*, 2022b). It was also revealed in the study that the various morphological characteristics of the species significantly influenced its phenolic and flavonoid compositions. Moncayo *et al.* (2021) also determined the TPC and TFC of ethanol extract of the aerial parts of *A. platyphyllum*, which contained TPC and TFC of 9.89 ± 0.02 (mg GAE/g dry extract) and 476.02 ± 12.35 (mg QE/g dry extract), respectively. They also conducted phytochemical screening on *A. platyphyllum*, showing that the ethanol extract of its aerial parts consisted of flavonoids, saponins, terpenoids, steroids, and tannins.

A rapid and reliable method based on high-performance liquid chromatography (HPLC) has been developed to determine the essential oils in *A. lavenia*. A total of 0.029% of essential oil was identified in the methanol extract of the branches and leaves of *A. lavenia* (Huyen *et al.*, 2019). Furthermore, these researchers successfully identified flavonoid compounds, such as quercetin, in another *Adenostemma* species, i.e., *A. viscosum*. The methanol extract of the branches and leaves of *A. viscosum* contained $0.067\% \pm 0.002\%$ quercetin and 1.24% essential oils.

Fauzan *et al.* (2018) established a simple and sensitive method, a profiling analysis approach using pyrolysis gas chromatography coupled with a mass spectrometer (Py-GCMS) to characterize the chemical composition of *A. lavenia* and *A. platyphyllum*. It was shown in the Py-GCMS results that 125 chemical components were present, including terpenoids, phenolics, alkaloids, and fatty acids. Epoxycyclododecane, 4-allyl-2,6-dimethoxyphenol, *cis,cis,cis*- 8,11,14-eicosatrienoic acid, tetradecahydroanthracene, and levoglucosan were the five most prominent substances overall. *N*-bearing compounds, alkaloids, aromatic compounds, terpenoids, and steroids predominated in *A. lavenia*. However, phenolic compounds and originated lipids (fatty acids) were the most prevalent chemicals in *A. platyphyllum*.

Several compounds have been successfully isolated from *Adenostemma* species. Bohlmann and Mahanta (1978) isolated germacrene D (Fig. 2A) and three kaurenoic acid derivatives (Fig. 2B–D) from an entire plant of *Adenostemma caffrum* extracted

Table 2. Chemical constituents found in *Adenostemma* species.

Plant Species	Plant Material	Group/Compounds	Extraction Methods and Compound Analysis	References
<i>A. lavenia</i>	Leaves, whole plant	Alkaloid, Essential oil	Maceration Qualitative phytochemical assay	Arthur, 2011
	Whole plant	11-hydroxylated kaurenoic acids: (A) ent-11 α ,15 α -dihydroxykaur-16-en-19-oic acid	Percolation, fractionation by column chromatography, and purification	Cheng <i>et al.</i> , 1979
		(B) ent-11 α -hydroxy-15 α -acetoxykaur-16-en-19-oic acid	Melting point, optical rotation, UV spectrophotometry, IR, mass spectrometry, NMR	
		(C) ent-11 α -hydroxy-15-oxo-kaur-16-en-19-oic acid (D) (16 <i>R</i>)-ent-11 α -hydroxy-15-oxokauran-19-oic acid	Reflux, fractionation by column chromatography, and purification	
Whole plant	Kaurane-type diterpenes: ent-11 α ,15 α -dihydroxykaur-16-en-19-oic acid; ent-11 α -hydroxy-15 α -acetoxykaur-16-en-19-oic acid; ent-11 α -hydroxy-15-oxo-kaur-16-en-19-oic acid; adenostemmoic acid A–G; Adenostemmoside A–G; paniculosides II and III.	Melting point, optical rotation, UV spectrophotometry, mass spectrometry, NMR, GC, and HPLC	Shimizu <i>et al.</i> , 1990	
<i>A. madurense</i>	Roots, stems, leaves	Alkaloid, terpenoid, steroid, phenolic (except stems)	Powdered plant Profiling analysis by pyrolysis GCMS	Fauzan <i>et al.</i> , 2018
	Branches and leaves	Essential oils	Maceration HPLC	Huyen <i>et al.</i> , 2019
	Leaves	Phenolic and flavonoid	Maceration UV-Vis spectrophotometry	Nurlela <i>et al.</i> , 2022b
<i>A. platyphyllum</i>	Leaves	Phenolic and flavonoid	Maceration UV-Vis spectrophotometry	Nurlela <i>et al.</i> , 2022b
	Roots, stems, and leaves	Phenolic, alkaloid (leaves), terpenoid, steroid (stems and leaves)	Powdered plant Profiling analysis by pyrolysis GCMS	Fauzan <i>et al.</i> , 2018
<i>A. brasilianum</i>	Aerial parts	Phenolic, flavonoid, saponin, terpenoid, steroid, and tannin	Maceration Qualitative phytochemical assay	Moncayo <i>et al.</i> , 2021
	Leaves	Phenolic and flavonoid	Maceration UV-Vis spectrophotometry	Nurlela <i>et al.</i> , 2022b
<i>Adenostemma caffrum</i>	Flowers and leaves	The ent-kauranes oxygenated at C-1, modified abietane, the eudesmane	Maceration, fractionation by column chromatography, and purification HPLC and NMR	Bardón <i>et al.</i> , 1996
	Whole plant	Germacrene D and the three kaurenoic acid derivatives	Extraction, fractionation by column chromatography, and purification Melting point, optical rotation, NMR	Bohlmann and Mahanta, 1978
<i>A. viscosum</i>	Branches and leaves	Quercetin	Maceration HPLC	Huyen <i>et al.</i> , 2019

with Et₂O-petrol. These kaurenoic acid derivatives were identical to the previously isolated compound from the *Eupatorium album*, another genus from Asteraceae (Herz and Sharma, 1976).

Cheng *et al.* (1979) also isolated four 11-hydroxylated kaurenoic acids from *A. lavenia*, namely ent-11 α -hydroxy-15 α -acetoxykaur-16-en-19-oic acid (Fig. 3A), ent-11 α ,15 α -dihydroxykaur-16-en-19-oic acid (11 α ,15OH-KA) (Fig. 3B), (16*R*)-ent-11 α -hydroxy-15-oxokauran-19-oic acid (Fig. 3C), and ent-11 α -hydroxy-15-oxo-kaur-16-en-19-oic acid (11 α OH-KA) (Fig. 3D). The compounds in Figure 2B and C were identical to a previously isolated compound from *A. caffrum* (Fig. 2B and D).

These compounds (Fig. 3A–D) were isolated from a whole plant of *A. lavenia* extracted with hexane and ethanol.

Furthermore, Shimizu *et al.* (1990) isolated kaurene-type diterpenes from *A. lavenia*. Three of the compounds were identical to those that Cheng *et al.* (1979) had previously reported (Fig. 3A, B, and D). Other 11-oxygenated kauran-19-oic acids were adenostemmoic acids A and B (1, 3) and their glycosides: adenostemmosides A and B (2, 4), paniculosides II and III (5, 6), adenostemmoic acid C–G (7, 9, 11, 13, 15), and their glycosides: adenostemmosides C–G (8, 10, 12, 14, 16), as depicted in Figure 4. These compounds were obtained from the methanolic extract of fresh plants, which were dissolved in water

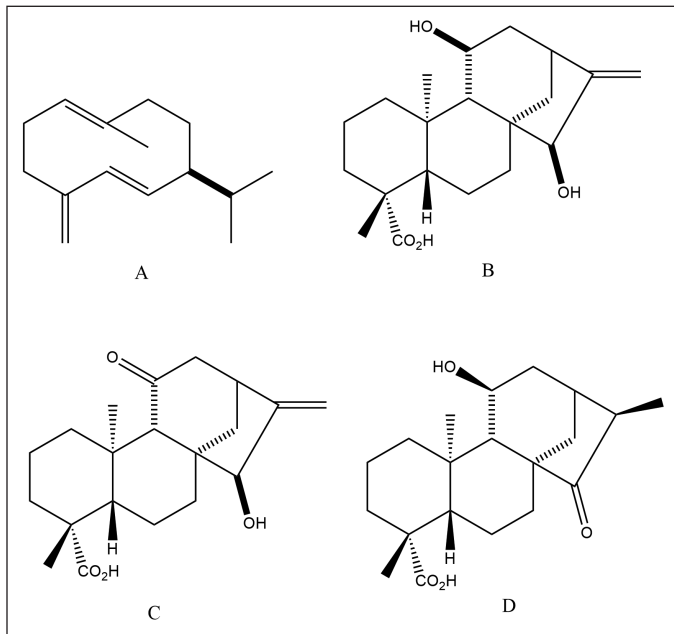


Figure 2. The compounds isolated from *Adenostemma cafferum*.

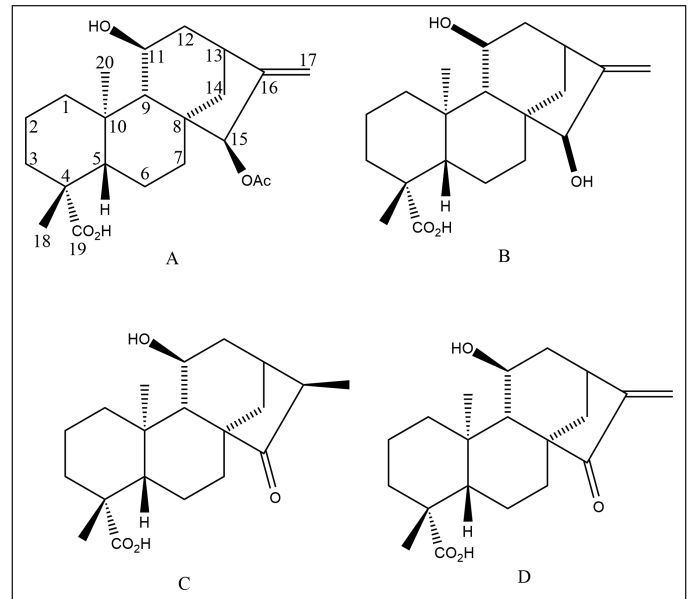


Figure 3. The structure of 11-hydroxylated kaurenoic acids isolated from *A. lavenia*.

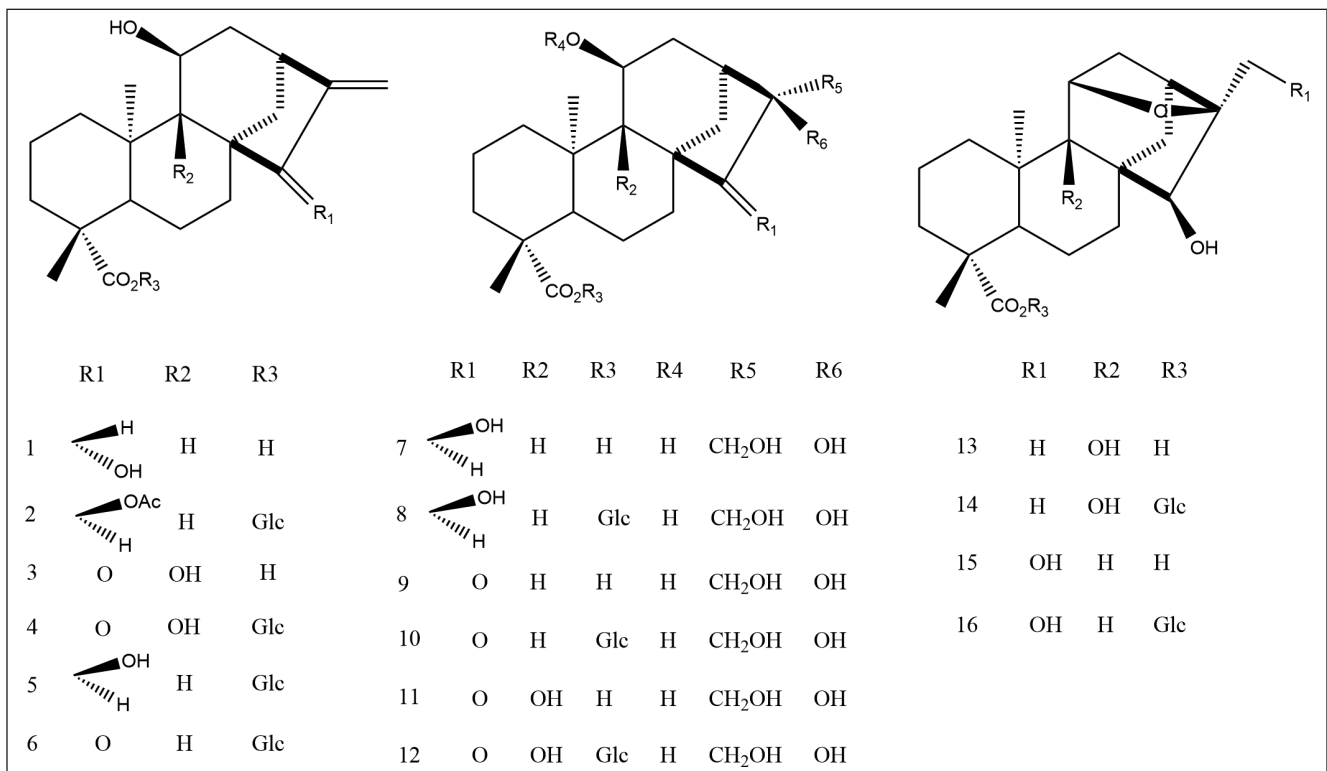


Figure 4. The kaurene-type diterpenes isolated from *A. lavenia*.

and extracted with ether. Hexane-benzene (1:1) and methanol-water (8:2) were used to partition the ether extract. The isolated compounds were characterized using various instruments, such as a spectrophotometer UV-Visible, spectropolarimeter, mass spectrometer, GC, HPLC, ¹H-NMR, and ¹³C-NMR. In addition to *A. lavenia*, several ent-kauranes oxygenated at C-1, a modified

abietane (Fig. 5A), and eudesmane (Fig. 5B) was also found in the aerial parts of *A. brasilianum* (Bardón *et al.*, 1996).

More recently, Maeda *et al.* (2022) successfully isolated three kaurenoic acids from another *Adenostemma* species, i.e., *A. madurense*, from Japan, and compared them with *A. lavenia* from Japan and the Taiwan region. They found that Japanese *A. lavenia*

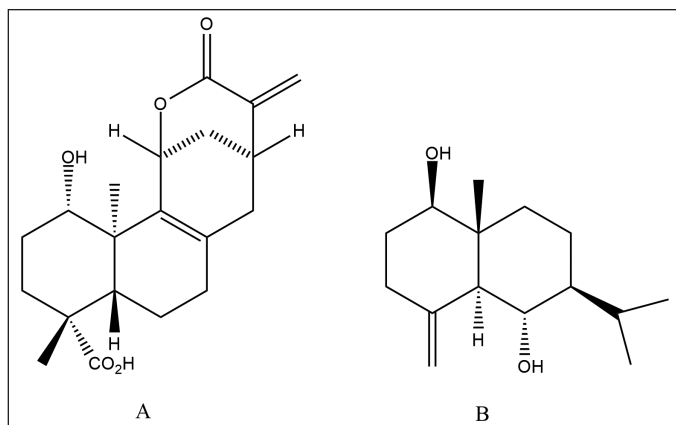


Figure 5. Abietane and eudesmane isolated from *A. brasilianum*.

and *A. madurense* had high amounts of ent-11 α -hydroxy-15-oxo-kaur-16-en-19-oic acid (11 α OH-KA) and moderate quantities of ent-11 α ,15 α -dihydroxykaur-16-en-19-oic acid (11 α ,15OH-KA). In contrast, Taiwanese *A. lavenia* mostly contained 9,11 α OH-KA (adenostemmoic acid B). The bioactivities of the compounds in *Adenostemma* will be discussed separately in the following section.

Pharmacological investigations

Numerous bioactivity studies of extracts and isolated compounds for their potential antioxidant, anti-inflammatory, and antimelanogenic properties have been motivated by the significant efficacy of *Adenostemma* species in traditional remedies. Here, we provide an overview of the notable pharmacological investigations of *Adenostemma* that have been reported in Table 3.

The crude extracts and isolated compounds from leaves, stems, roots, and whole plants of the *Adenostemma* species demonstrate various biological activities. The leaf has been extensively studied compared to the stem and root. The pharmacological activities discussed in this review include antioxidant, anti-inflammatory, antimelanogenic, antitumor, and antiviral activities.

Antioxidant activity

Antioxidants are substances that can prevent the formation of free radicals through several mechanisms. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are two common forms of radicals. In general, free radicals are produced due to the influence of internal and external factors. External factors include pollution and cigarette smoke, while internal factors include intracellular metabolism (Pizzino *et al.*, 2017; Sharifi-Rad *et al.*, 2020).

ROS and RNS are produced by intracellular metabolism as byproducts of the cellular redox reaction that occurs when adenosine triphosphate is formed to provide energy for the cells by consuming oxygen. When in balance, immunological responses and cellular functions are supported by ROS and RNS. However, unbalanced ROS and RNS concentrations result in oxidative stress, potentially causing chronic and degenerative diseases (Tungmunthum *et al.*, 2018). Many natural antioxidant compounds have been used as substitutes for synthetic antioxidants

in medical and pharmaceutical applications, considering that natural compounds are less toxic (Sharifi-Rad *et al.*, 2020).

Some *Adenostemma* species have been evaluated for antioxidant activity using several methods. Generally, *in vitro* assay of antioxidant activity used diphenyl-2-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) to quantify the radical-scavenging activity or measure ferric reducing antioxidant power and cupric ion reducing antioxidant capacity assay based on redox reaction. The antioxidant activity of the water extract of whole plant *A. lavenia* was determined using DPPH and ABTS methods, resulting in inhibition percentage, IC₅₀ DPPH, and ABTS of 91.28% \pm 1.39%, 121.82 \pm 15.84 μ g/ml, 3.38 \pm 0.17 mg TE/g extract, respectively (Budiarti *et al.*, 2019).

Batubara *et al.* (2020) reported that the antioxidant activity of *A. lavenia* leaves reached an IC₅₀ value of 252.02 \pm 3.23 μ g ml⁻¹, ABTS of 3.63 \pm 0.41 mg trolox/g sample (water fraction) and IC₅₀ value of 222.37 \pm 1.16 μ g ml⁻¹, ABTS of 3.24 \pm 0.39 mg trolox/g sample (chloroform fraction). The antioxidant activity in *A. platyphyllum* has also been investigated, resulting in inhibition percentage and IC₅₀ of 77.50 \pm 0.39 and 1.60 mg ml⁻¹, respectively, in the ethanol extract of aerial plant parts (Moncayo *et al.*, 2021).

In addition to radical-scavenging activity, an antioxidant activity assay can be conducted on cellular levels *in vitro*. In a concentration-dependent way, *A. lavenia* extracts and ent-11 α -hydroxy-15-oxo-kaur-16-en-19-oic acid (11 α OH-KA) isolated from *A. lavenia* CHCl₃ leaves extract increased the yeast lifespan and provided *Schizosaccharomyces pombe* and B16F10 cells with resistance to H₂O₂. 11 α OH-KA stimulated the production of heme oxygenase-1 (HO-1) and the antioxidative transcription factor nuclear factor-E2-related factor 2 (Nrf2), a mammalian homolog of pap1+, in B16F10 cells (Batubara *et al.*, 2020). More recently, Maeda *et al.* (2022) reported that Nrf2 and HO-1 protein levels were increased by 11 α OH-KA, 9,11 α OH-KA in a dose-dependent manner but not by 11 α ,15OH-KA in RAW 264.7 cells. These kaurenoic acids were isolated from the CHCl₃ fraction of *A. lavenia* and *A. madurense*.

Anti-inflammatory activity

Inflammation is a normal response of the immune system to protect tissues from infection, injury, or disease. Various factors, such as pathogens, noxious substances, damaged cells, and ingested toxins, can trigger such a process (Chen *et al.*, 2018). These factors induce acute or chronic inflammatory reactions in the body that may lead to many illnesses, such as arthritis, heart disease, lung injury, atherosclerosis, metabolic syndrome, allergies, and other autoimmune disorders, and a pathological component of cancer (Chen *et al.*, 2019; Gonçalves and Romano, 2016; Gonçalves and Romano, 2016; Vogl *et al.*, 2013). Inflammation can be activated by various mediators, including cytokines, such as bacterial endotoxins or lipopolysaccharide (LPS), nitric oxide (NO), and prostaglandins, which are produced from the metabolism of arachidonic acid catalyzed by the cyclooxygenase-2 (COX-2) enzyme (Tuwalaid *et al.*, 2022; Wang *et al.*, 2019).

Several investigations have been conducted to assess the anti-inflammatory properties of *Adenostemma* species. Chen *et al.* (2019) investigated the anti-inflammatory effects of ethyl

Table 3. Pharmacological investigation of *Adenostemma* species.

Plant	Extract/compound	Bioactivities	References
<i>Adenostemma lavenia</i>	The compound isolated from MeOH whole plant extract: (A). ent-11 α -hydroxy-15-oxo-kaur-16-en-19-oic acid; (B). Adenostemmoic acid B	Antitumor activity with low nonspecific cytotoxicity activity against L5178Y leukemia cells and prolonged the survival of mice implanted with sarcoma-180 (ID ₅₀ of 2.8 μ g/ml; 163%; dose of 100 mg/kg \times 5 days for (A) compound; and ID ₅₀ of 4.2 μ g/ml; 178%; dose of 100 mg/kg \times 5 days for (B) compound)	Shimizu <i>et al.</i> , 1990
	Water extract of the whole	Antioxidant (DPPH: IC ₅₀ of 121.82 μ g/ml; ABTS: 3.38 mg TE/g extract) Antiglycation (inhibition of 87.87% from 1,000 μ g/ml extract)	Budiarti <i>et al.</i> , 2019
	A compound isolated from ethyl acetate fraction of the whole plant: p-coumaric acid	Anti-inflammatory (NO inhibitory activity: IC ₅₀ of 101.49 μ g/ml in LPS-activated macrophages)	Chen <i>et al.</i> , 2019
	CHCl ₃ leaves extract and compound isolated: ent-11 α -hydroxy-15-oxo-kaur-16-en-19-oic acid (11 α OH-KA)	Antioxidant • Water fraction DPPH: IC ₅₀ of 252.02 \pm 3.23 μ g ml ⁻¹ ; ABTS: 3.63 \pm 0.41 mg trolox/g sample • CHCl ₃ fraction DPPH: IC ₅₀ 222.37 \pm 1.16 μ g ml ⁻¹ ; ABTS: 3.24 \pm 0.39 mg trolox/g sample	Batubara <i>et al.</i> , 2020
	Water leaves extract	Antiglycation (% inhibition of 1,000 μ g ml ⁻¹ sample): Water fraction: 8.87 \pm 2.28 and CHCl ₃ fraction: 33.44 \pm 4.87 Antimelanogenic against B16F10 melanoma cells (9 μ g/ml with inhibition of 100%), and suppress hair pigmentation in mice (0.3 mg/ml)	Hamamoto <i>et al.</i> , 2020
<i>A. madurense</i>	The compound isolated from CHCl ₃ leaves extract: 9,11 α OH-KA and 11 α OH-KA	Antimelanogenic Anti-inflammatory Antioxidant	Maeda <i>et al.</i> , 2022
	The compound isolated from CHCl ₃ leaves extract: Adenostemmoic acid B	Anti-inflammatory Antimelanogenic	Kobayashi <i>et al.</i> , 2022
	The compound isolated from CHCl ₃ leaves extract: 9,11 α OH-KA and 11 α OH-KA	Antimelanogenic Anti-inflammatory Antioxidant	Maeda <i>et al.</i> , 2022
<i>A. platyphyllum</i>	Ethanol extract of aerial part	Antioxidant (DPPH: % Inhibition = 77.50 \pm 0.39 IC ₅₀ = 1.60 mg ml ⁻¹)	Moncayo <i>et al.</i> , 2021
<i>The genus Adenostemma</i>	Ent-6-11-dihydroxy-15-oxo-16-kauren-19-oic acid β -D-glucopyranosyl ester and adenostemmosides B	Antivirals (<i>in silico</i>)	Nurlela <i>et al.</i> , 2022a

acetate fractions of *A. lavenia* (EAAL) *in vitro* and *in vivo*. These researchers revealed that EAAL decreased proinflammatory cytokine responses, with 4-hydroxycinnamic acid (*p*-coumaric acid) as its principal constituent. It was also reported in this study that EAAL inhibited COX-2 and protein expression of inducible NO synthase (iNOS), phosphorylation of I κ B- α , MAPKs, and AMP-activated protein kinase, activated HO-1, and Nrf2 in LPS-stimulated cells and lung tissues, and antioxidant enzymes (catalase, SOD, and GPx).

Furthermore, Maeda *et al.* (2022) demonstrated that isolated kaurenoid acids, 11 α OH-KA and 9,11 α OH-KA had an anti-inflammatory effect by reducing NO production in LPS-stimulated RAW 264.7 cells, decreasing iNOS protein levels, and suppressing the transcript levels of proinflammatory molecules (IL-6 and TNF α). At the same time, 11 α and 15OH-KA did not have any appreciable inhibitory effects.

Recently, Kobayashi *et al.* (2022) succeeded in separating antimelanogenic, anti-inflammatory, and cytotoxic activities by altering the 19th position of 9,11 α OH-KA or adenostemmoic acid B (AB) (carboxy implicated in the avoidance of cytotoxicity). NO synthesis and iNOS expression were suppressed by long-chain alkylation (hydrophobic) without an antimelanogenic effect. At doses greater than 3 μ M, AB inhibited NO production in RAW264.7 cells. Surprisingly, NO production was effectively reduced by the hydrophobic derivatives, hexyl and octyl, at lower concentrations of 1 and 0.3 μ M, respectively.

Antimelanogenic activity

Melanogenesis, which results in the creation of melanin, the primary pigment responsible for human skin, eye, and hair coloring, is crucial for shielding the skin from UV radiation (D'Mello *et al.*, 2016; Pillaiyar *et al.*, 2018). However, the overproduction of melanin (hyperpigmentation) is linked to

various human disorders, such as freckles, melasma, age spots, and pigmented acne scars (Avcil *et al.*, 2021; Kumarasinghe, 2018). Therefore, antimelanogenic compounds are usually used to counter hyperpigmentation. 11OH-KA, which is present in the leaves of *Adenostemma* and plants from another genus of Asteraceae, such as *Pteris* and *Gochmatia*, is a promising candidate for antimelanogenic drugs (Kuroi *et al.*, 2017) excess melanin can be undesirable, particularly on the face where spots or freckles are associated with an appearance of aging. In this study, we found that ent-11 α -hydroxy-15-oxo-kaurene-16-en-19-oic acid (11 α -OH KA).

Melanogenesis is prevented by 11 α OH-KA by suppressing tyrosinase gene expression. The conversion of L-tyrosine to L-DOPA (L-3,4-dihydroxyphenylalanine) is catalyzed by tyrosinase, the rate-limiting enzyme in melanin production in melanocytes. L-3,4-dihydroxyphenylalanine is oxidized to DOPA-quinone (Yardman-Frank and Fisher, 2021). Hamamoto *et al.* (2020) demonstrated the potential of *Adenostemma* plants for antimelanogenesis in an *in vivo* study. They discovered that mice treated with an aqueous extract of an *A. lavenia* leaf containing a high amount of 11 α OH-KA had decreased pigmentation in hair. Additionally, 9,11 α OH-KA contained in *A. lavenia* and *A. madurense* has an antimelanogenic effect by suppressing the expression of the tyrosinase gene (Maeda *et al.*, 2022). Furthermore, the short-chain alkylation of the carboxy group of 9,11-OH-KA increased its antimelanogenic effects. In contrast, NO synthesis and iNOS expression were inhibited by long-chain alkylation, but did not have antimelanogenic effects (Kobayashi *et al.*, 2022).

Other bioactivities

The antiproliferative activities of extracts from *A. lavenia* and the pharmacological activities mentioned above have been shown in other investigations. Both 11 α OH-KA and 9,11-OH-KA were isolated from methanol extracts of entire *A. lavenia* plants and had antitumor efficacy with low nonspecific cytotoxicity activity against L5178Y leukemia cells. Additionally, the longevity of mice implanted with sarcoma-180 was increased by these substances (Shimizu *et al.*, 1990).

11 α OH-KA and 9,11-OH-KA are some diterpenoids found not only in *Adenostemma* species, but also in other plants, such as *Plectranthus asirensis* and *Pteris semipinnata* L. These substances have antioxidant, anti-inflammatory, anticancer, and antitumor activities (Lu *et al.*, 2013; Saeed *et al.*, 2020). Other diterpenoids, such as brianthine V, are isolated from *Briareum asbestinum* and have cytotoxic and antiviral activities (Coval *et al.*, 1988). It was revealed in a recent study that the expression of the antioxidant protein heme oxygenase (HO-1) could be promoted by 11 α OH-KA isolated from *A. lavenia* through the transcription of factor Nrf2 in mouse melanoma cells (Batubara *et al.*, 2020). The activation mechanism of the HO-1-Nrf2 antioxidant gene is currently suggested as a cellular target for curing COVID-19 sufferers (McCord *et al.*, 2020). The kaurene diterpene glycoside ent-6-11-dihydroxy-15-oxo-16-kauren-19-oic acid β -D-glucopyranosyl ester and adenostemmosides B were exhibited in our recent study about the *in silico* of some kaurene diterpenoids. Plants in the *Adenostemma* genus were also found to have inhibitory activities on the nonstructural and structural

proteins of SARS-CoV-2 virus (Nurlela *et al.*, 2022a). It was also shown by the investigation that the ligands were firmly bounded to the binding sites of the proteins, achieved stability, were well absorbed by the human intestine and noncarcinogenic substances, and did not lead to DNA changes. We expect that these substances might have promise as preventative and therapeutic agents in the battle against COVID-19 disease.

CONCLUSION

The traditional uses, chemical compounds, and pharmacological studies covered in this review demonstrated that the accumulation of bioactive compounds in various *Adenostemma* species widely utilized in traditional medicine might account for the observed health-promoting effects. *Adenostemma lavenia*, *A. madurense*, and *A. platyphyllum* were the most frequently reported species in the genus *Adenostemma*. In recent years, there has been a significant advancement in scientific knowledge of plant chemical compounds and biological activities. However, numerous species in the genus have yet to be thoroughly characterized, suggesting that further investigation is needed. Although several bioactivities of *Adenostemma* have been investigated, the chemical compounds in *Adenostemma* may have other bioactivities that still need to be discovered and evaluated. According to the explanation in the current review article, crude extracts or isolated compounds of *Adenostemma* have various pharmacological properties that have been demonstrated by *in vitro*, *in vivo*, and *in silico* test results, making *Adenostemma* one of the plants with the potential to be developed in discovering new drugs.

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AUTHORS CONTRIBUTIONS

All of the authors have made a significant contribution to this manuscript. Concept and design were done by IB and HT. Data acquisition and analysis/interpretation were done by NN and B. Drafting manuscript is done by NN. Critical manuscript revision is carried out by IB, WN, AI, and NN. Supervision and final approval is done by IB. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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