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Submission date: 05-Apr-2022 01:34PM (UTC+0700)
Submission ID: 1802233419
File name: Full_Paper_Review_Paper_JAPS_1.pdf (606.79K)
Word count: 6967
Character count: 40276

Journal of Applied Pharmaceutical Science Vol. 12(04), pp 170-178, April, 2022
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2022.120419
ISSN 2231-3354

Ethnopharmacology, phytochemistry, and biological activity review of *Aleurites moluccana*

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ARTICLE INFO

Received on: 11/10/2021
Accepted on: 16/01/2022
Available Online: 05/04/2022

Key words:
Aleurites moluccana, ethnopharmacology, phytochemistry, biological activity, secondary metabolite, local wisdom.

ABSTRACT

Since ancient times, the sustained use of *Aleurites moluccana* in folk medicine has been described verbally and in written manuscripts as a part of local wisdom. Diverse cultures across the world have traditionally used multiple portions of these plants to cure various illnesses, including headaches, fever, asthma, injuries, stomach ulcers, and tumors. Recent scientific discoveries provide insight on the chemical and biological basis for this species' broad medicinal application. According to data from Google Scholar, Science Direct, ProQuest, Scopus, and PubMed, at least 34 compounds have successfully been purified and characterized from *A. moluccana* over the last several decades, consisting of coumarinolignoid, C-glycosyl-flavone, phorbol diester, sterol, diterpene, triterpene, coumarin, and aliphatic hydrocarbon derivatives. Additionally, extracts and secondary metabolites from this species exhibited interesting biological properties, including antibacterial, cytotoxic, anti-inflammatory, and antinociceptive effects. To the authors' knowledge, this is the first concise review covering current reports on the ethnopharmacology, phytochemistry, and biological activity of *A. moluccana*.

INTRODUCTION

Local wisdom has been demonstrated to be a powerful instrument revitalized globally, particularly in Asia, for promoting health across a diverse range of societies (Demaio, 2011). For millennia, many medicinal remedies based on indigenous wisdom have been conveyed, transferred, and inherited from generation to generation. In 2006, according to the World Health Organization, traditional medicine was used by 80% of people globally, while 25% of contemporary medications are derived from traditionally used medicinal herbs (Maurya and Gupta, 2006). Therefore, extensive ethnobotanical investigations have been carried out and resulted in discovering novel chemical compounds applied in modern medicine (Situmorang *et al.*, 2015).

Among the existing popular folk medicines, *Aleurites moluccana*, also known as "candlenut" or "kemiri nut" (Zakaria *et al.*, 2019), has been one of the most promising sources of drug candidates due to its convenient availability and ability to produce a diverse array of secondary metabolites with interesting biological activities. Heretofore, *A. moluccana* leaves have been employed as poultices, including for contusions and swelling (Elevitch and Manner, 2006), and to cure asthma, stomach ulcers, headaches, fever, and hepatitis (Hoepers *et al.*, 2015). The seed oil is mainly applied as a laxative as well as for hair treatment and worm eradication (Rojas-Sandoval *et al.*, 2019). Additionally, this species is used medicinally to treat cardiovascular diseases, anemia, cholesterol, hypertension, and diabetes (Hidayat *et al.*, 2021). Based on these local cultures, extensive research has been conducted to identify secondary metabolites with excellent bioactivity, including but not limited to antinociceptive, antimicrobial, cytotoxic, and anti-inflammatory properties.

To the authors' knowledge, a comprehensive overview on the exploration of *A. moluccana*'s cultural use, chemical investigation, and activity assessment has barely been reported. Hence, we have critically compiled and analyzed numerous studies on this species' ethnopharmacology, phytochemistry, and biological activity. Given the tremendous potential revealed

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in this work, it is hoped that research on the isolation, structural elucidation, and biological activity evaluation of *A. moluccana* metabolites can be expanded. In addition, we wish that this report could attract more natural product researchers to prospect local wisdom-based drug discovery in the future.

SPECIES DESCRIPTION

Aleurites moluccana (L.) Willd. was classified taxonomically as a part of the genus *Aleurites* (family: Euphorbiaceae, order: Archichlamydeae) (Shaah *et al*., 2021) together with another species that shares "candlenut" as a common name, *Aleurites rockinghamensis* (Rozefelds *et al*., 2017). This species was initially cultivated in Indo-Malaysia before being introduced throughout the Pacific Islands. It now has a wide geographical distribution throughout the world, including but not limited to Sri Lanka, Bangladesh, India, Brazil, Puerto Rico, Madagascar, the Virgin Islands, and the West Indies, as well as the United States (Elevitch and Manner, 2006). It is ubiquitous in tropical monsoon climatic zones, particularly those above 1,200 m from sea level, and proliferates on slopes. *Aleurites moluccana* is frequently found in regions with average temperature of 18°C–28°C and rainfall of 640–4,290 mm every year. This plant is adaptable to many kinds of soils with a pH of 5–8 and prefers whole light and is highly resistant to drought. *Aleurites moluccana* has a delicate tree trunk with a red coloring substance in the bark. This species produces olive-colored round fruits with two cells, each carrying one seed. It is a monoecious plant, with female and male blooms growing separately on the same tree. The white and obtuse flower has five petals, 2–3 valvate lobes, and 8–30 stamens of varying lengths grouped in terminal panicled cymes. Additionally, this tree has alternating and ovate acute leaves that are 4–8 in length and possess a long extensive petiole and are pubescent, as well as 3–7 lobes (Krisnawati *et al*., 2011).

ETHNOPHARMACOLOGY

Aleurites moluccana has been extensively employed in traditional folk medicine by various tribes worldwide as a component of their local wisdom. This medicinal plant's expertise is passed down verbally or through old manuscripts. This species has been widely used in Indonesia as one of the traditional remedies passed down through generations and kept as a cultural treasure. Usada, a traditional plant-based medicinal book written in palm leaves by one of the ethnic groups in Indonesia called Sasak, described this herb's usage for diarrhea and pregnant chants (Yamin and Burhanudin, 2018). Additionally, indigenous healers of this ethnic group prescribe this herb for asthma, stomach problems, skin ulcers, poisoning recovery, and swollen wombs (Fadila *et al*., 2021). In general, the local community in Indonesia utilizes the bark of *A. moluccana* to cure dysentery (Suwardi *et al*., 2020), diarrhea (Romulo *et al*., 2018), and typhoid fever (Prabowo and Agustina, 2020). Apart from lighting and culinary uses, seed oil has been used medicinally in Indonesia as a laxative (Susilowati *et al*., 2020), as well as a cure for wounds (Yamlean *et al*., 2019) and children protuberance (Dalya and Mujetahid, 2020). This oil can be produced by removing, crushing, and roasting the fruit (Giesen, 2021). In the laboratory, the oil may be effectively and efficiently acquired by immersing this sample in a suitable solvent, such as methanol, and collecting the extracted oil after achieving the equilibrium extraction (Faiznur and Wan, 2019) or by Soxhlet extraction using hexane as a solvent (Zouarhi *et al*., 2019). According to Bai *et al*. (2020), the seed can also treat colds and coughs. Additionally, Indonesians use the leaves to heal high cholesterol (Jaya *et al*., 2019).

Diverse populations from different nations have also used various parts of *A. moluccana* as ingredients in traditional remedies from ancient times (Ismail *et al*., 2018). In Malaysia, the seeds of this plant are combined with many other plants to treat a baby's fever. Furthermore, they apply the kernel to a specific body area to alleviate ulcers, swollen joints, headaches, and fever (Lim, 2012). This part is also beneficial for cleaning a newborn's throat. In this country, the leaves are used to cure headaches, coughs, chest pain, fever, ulcers, diarrhea, gonorrhea, and hernias.

Meanwhile, in Japan, this plant's bark is utilized to treat tumors (Prabowo *et al*., 2013). Traditionally, the seeds have been processed to make laxatives, purgatives, hair fertilizers, and castor oil (Abd and Mohamad, 2010). Furthermore, ancient Papua New Guinea medicine used the seeds as a contraceptive by physically applying them to the male genitals. They also utilized the bark to relieve food poisoning and constipation (Prasad *et al*., 2011).

In Hawaii's agroforestry social-ecological system, *A. moluccana* is one of the most prevalent crops (Winter *et al*., 2018). Due to its distinctive beauty and centuries-old usage as fuel, dye, decoration, illumination, and medicine, it has become the national tree of Hawaii (Elevitch and Manner, 2006). This tree was also a staple of the medical cornucopia, since the oil and sap were used to treat insect bites, aphthous ulcers, and other skin conditions; the leaves were used to patch wounds; while the shell was used to treat hearing, smelling, and throat problems (Lincoln *et al*., 2021). The indigenous people of this region utilize the sap to treat scars and certain skin conditions (Cesca *et al*., 2012). Moreover, the Polynesians possessed an exceptional ability to employ local flora for medicinal purposes. The bark is employed to heal wounds in the western part of Samoa (Prasad *et al*., 2011). The folk medicines in the Cook Islands apply the seeds to dress stab wounds and flowers to remove the pus. In general, Pacific Islands, including Fiji, Samoa, Tonga, Tahiti, and Hawaii, mainly employ the seeds of this species for infection, conjunctivitis, vaginal discharge, and skin problems; the barks for skin inflammation; the flowers for scalp care; the fruits for abrasions on the scalp, toothaches, and corneal abrasions; the sap for conjunctivitis and skin conditions; and the leaves for infections and swellings (Hughes *et al*., 2019).

The local community in Brazil practice traditional medical treatment for rheumatic diseases using the seeds of *A. moluccana* (Quintão *et al*., 2014). The leaves are also given to people suffering from hepatitis, asthma, gastric ulcers, fever, headaches, and inflammation (Hoepers *et al*., 2015). In China, a remedy for sprue and thrush is a mixture of stem bark of this plant and coconut milk. The fruit is utilized externally to treat fever, rheumatoid arthritis, skin problems, ulcers, and headaches. Moreover, the seeds are used to treat constipation by burning them with charcoal and can alleviate sciatic pain by oil extraction (González-Stuart and Rivera, 2019). In India, the oil is employed to treat ulcers, while in the Philippines the seeds are utilized as purgatives (Lim, 2012).

PHYTOCHEMISTRY

After learning from the local wisdom of folk medicine in the revitalization of *A. moluccana* as a cure, immense research

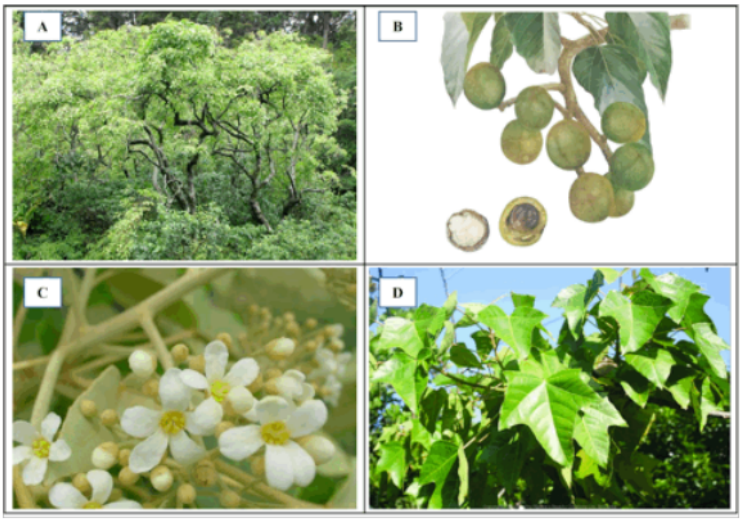

Figure 1. (A) Tree of *A. moluccana* in natural habitat (source: Dixon *et al.*, 2019). (B) Fruit of *A. moluccana* (source: Center for International Forestry Research (CIFOR) team, 2021). (C) Flower of *A. moluccana* (source: Health Benefits Times team, 2021). (D) Leaves of *A. moluccana* (source: Natures Beauty Creations team, 2015).

in the investigation of drug candidates from these species has been conducted. This endeavor resulted in the identification of many compounds with potential pharmacological activity. From a nutritional aspect, this species has been found to contain calories, carbohydrates, protein, dietary fiber, riboflavin, trace amounts of niacin, thiamin, and vitamin E, as well as minerals such as sodium, potassium, calcium, magnesium, iron, and zinc (Lim, 2012). In addition, the appearance of 11 fatty acids was discovered in gas-liquid chromatography analysis of the seed oil, with linolenic acid being the most abundant (49.55%) (Sapna, 2015). *Aleurites moluccana* also includes a few unfavorable compounds, such as toxalbumin, which might influence blood agglutination and induce blood clotting. However, a moist heating treatment followed by drying may reduce the toxicity of the contained glycoproteins (Bilang *et al.*, 2018)

Interestingly, diverse secondary metabolites have been detected in this sample. Based on data collected from electronic archives in Google Scholar, Science Direct, ProQuest, Scopus, and PubMed, at least 34 metabolites were isolated and identified from *A. moluccana* in the last three decades (1988–2020). Shamsuddin *et al.* (1988) isolated a coumarinolignoid, moluccanin (**1**), from ethanol extracts of the stem chips. Swertisin (**2**) and 2″-O-rhamnosylswertisin (**3**) were purified from the leaves of this species and identified as C-glycosyl-flavone derivatives (Meyre-Silva *et al.*, 1997, 1999). Meanwhile, Satyanarayana *et al.* (2001) worked with the heartwood to provide a phorbol diester, 13-*O*-myristyl-20-*O*-acetyl-12-deoxyphorbol (**4**). Moreover, stigmasterol, *β*-sitosterol, campesterol, and *β*-sitostenone were sterol derivatives obtained from different parts of this plant (Meyre-Silva *et al.*, 1998; Satyanarayana *et al.*, 2001). Purification of the acetone extract from the branch and leaf of this species provided 11 diterpenes which were identified as (5*β*,10*α*)-12,13-dihydroxypodocarpa-8,11,13-trien-3-one (**5**), (5*β*,10*α*)-12-hydroxy-13-methoxypodocarpa-8,11,13-trien-3-one (**6**), (5*β*,10*α*)-13-hydroxy-12-methoxypodocarpa-8,11,13-trien-3-one (**7**), (3*α*,5*β*,10*α*)-13-methoxypodocarpa-8,11,13-triene-3,12-diol (**8**), 12-hydroxy-13-methylpodocarpa-8,11,13-trien-3-one (**9**), spruceanol-12 (**10**), *ent*-3*α*-hydroxypimara-8(14),15-dien-12-one (**11**), *ent*-3*β*,14*α*-hydroxypimara-7,9(11),15-triene-12-one (**12**), moluccanic acid (**13**), moluccanic acid methyl ester (**14**), and 6,7-dehydromoluccanic acid (**15**) (Alimboyoguen *et al.*, 2014; Liu *et al.*, 2007, 2008).

Fascinatingly, the separation of *A. moluccana*'s stem bark gave one triterpene, 3-acetylaleuritolic acid (**16**) (Alimboyoguen *et al.*, 2014), while that of the leaves yielded five additional triterpenes, *α*-amyrin, *β*-amyrin, *α*-amyrenone, *β*-amyrenone, and glutinol (Meyre-Silva *et al.*, 1998). Scopoletin (**17**) obtained from the stem bark (Prabowo *et al.*, 2013) and 6,7-dimethoxycoumarin and 5,6,7-trimethoxycoumarin attained from the heartwood were classified as coumarins. Satyanarayana *et al.* (2001) also obtained an aliphatic carbon chain, hentriacontane, from the separation of the heartwood. Furthermore, da Silva *et al.* (2012) reported that five megastigmanes, namely, vomifoliol-9-*O*-β-apiofuranosyl-(1″→6′)-β-glucopyranoside (**18**), (6*S*,9*R*)-roseoside (**19**), debiloside (**20**), 3-Oxo-α-ionol-*O*-β-apiofuranosyl-(1″→6′)-β-glucopyranoside (**21**), and 3-Oxo-α-ionol-*O*-β-glucopyranoside (**22**), were obtained from the leaves. Some selected structures of the purified compounds from *A. moluccana* were drawn in Figure 2.

BIOLOGICAL ACTIVITY

The ability of *A. moluccana* to heal multiple ailments, as apprised in local wisdom, could be a result of its biological activities. Numerous studies reported that extracts and secondary metabolites from this species displayed fascinating biological characteristics, including antibacterial, cytotoxic, anti-inflammatory, and antinociceptive effects. The following sections outline different pharmacological research on this species.

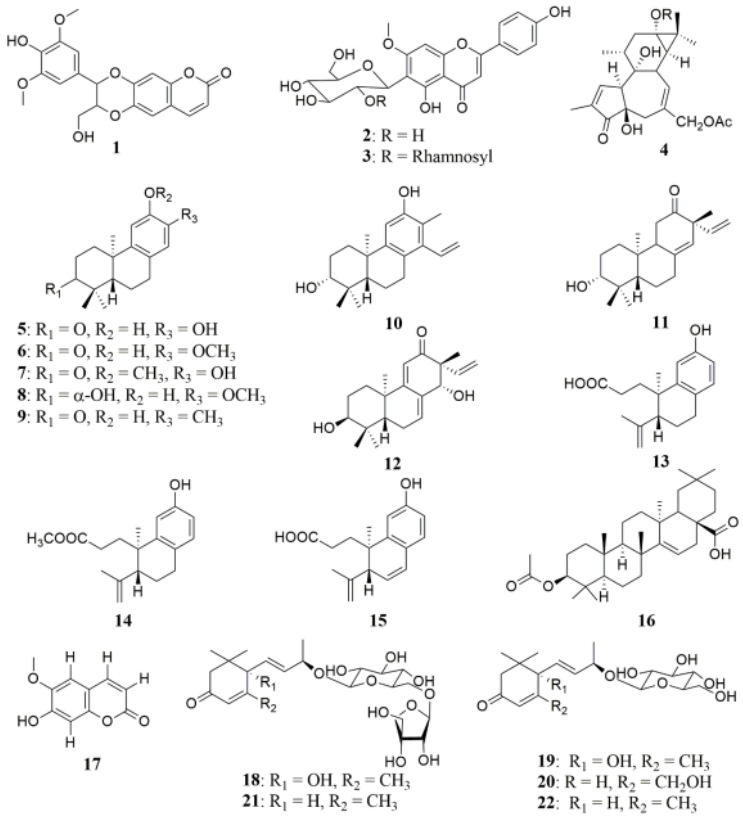

Figure 2. Structures of some selected compounds from *A. moluccana*.

Antimicrobial activity

The importance of developing novel antimicrobials has increased significantly due to the rising demand for antibiotics used to treat bacterial infections and the emergence of antibiotic resistance (Arora and Kaur, 2007). Numerous studies on the antibacterial activities of plant extracts and secondary metabolites have been undertaken worldwide to meet these needs (Prusti, 2008). Extracts and substances from plants that exhibit these characteristics should be subjected to additional testing against many bacterial strains to validate their activity and identify the associated parameters, as bacteria may show varying degrees of sensitivity to the same chemical (Nair *et al.*, 2005). Antibacterial activity is quantified by MIC standing for minimum inhibitory concentration, the smallest sample quantity needed to prevent observable growing (Ningsih *et al.*, 2021).

The bark ethanol extract from this plant possessed antimicrobial characteristics against *Candida albicans* and *Staphylococcus aureus* in the equal MIC values of 256 µg/ml as well as on *Enterococcus faecalis* with a MIC of 512 µg/ml (Romulo *et al.*, 2018). The bark methanol extract exhibited bacterial growth inhibition against *S. aureus*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* with the MIC values of 390, 781, and 98 µg/ml, respectively (Abd and Mohamad, 2010). The *A. moluccana* nut methanol extract showed antibacterial activity against bacteria that stimulate rheumatoid arthritis with the MIC values of 215 and 438 µg/ml for experimental and standard *Proteus mirabilis* strains, respectively, and a MIC value of 187 µg/ml for *Proteus vulgaris*. In addition, it displayed the same activity on *Klebsiella pneumoniae* and *S. pyogenes* growth with equal MIC values of less than 1,000 µg/ml. The ethyl acetate and aqueous extracts also indicated high antibacterial activity with even slightly higher values of MIC (Mpala *et al.*, 2017). Furthermore, the methanol extract partially inhibited quorum sensing-dependent pigmentation of *Chromobacterium violaceum*, which may be a result of its bioactive constituents, especially flavonoid, terpenoid, and phenolic derivatives (Guzman and Padilla, 2017).

The *A. moluccana* oil derivatives also had antibacterial properties. For instance, 1% of the "potassium soap," "fatty acids," and "methyl esters" showed this bioactivity on *S. aureus* with inhibition zone diameters of 12.07, 8.75, and 6.67 mm, respectively, along with on *Escherichia coli* with inhibition zone diameters of 12.18, 11.02, and 7.32 mm, respectively. Meanwhile, 2% of those substances displayed antibacterial properties on *S. aureus* with inhibition zone diameters of 13.20, 9.77, and 7.33 mm, respectively, and on *E. coli* with inhibition area diameters of 14.00, 13.23, and 8.70 mm, respectively (Sutrisno *et al.*, 2020). Furthermore, compound **7** separated from the bark displayed potent antibacterial characteristics on *Salmonella typhimurium* at 250 µg/ml (Prabowo *et al.*, 2013).

Table 1. Ethnopharmacological uses of *A. moluccana*.

Place	Part(s) used	Ethnopharmacological uses	Reference(s)
Indonesia	Bark	Dysentery, diarrhea, and typhoid fever	Suwardi *et al.* (2020); Romulo *et al.* (2018); Prabowo and Agustina, (2020)
	Seed	Laxative, wounds, children protuberance, colds, and cough	Susilowati *et al.* (2020); Yamlean *et al.* (2019); Dalya and Mujetahid, (2020); Bai *et al.* (2020)
	Leaf	Cholesterol	Jaya *et al.* (2019)
Malaysia	Seed	Fever in babies	Lim, (2012)
	Kernel	Ulcers, swollen joints, headaches, and fever and clear the throats of newborns	
	Leaf	Headaches, cough, chest pain, fever, ulcers, diarrhea, gonorrhea, and hernias	Prabowo *et al.* (2013)
Papua New Guinea	Seed	Contraceptive	Prasad *et al.* (2011)
	Bark	Food poisoning and constipation	
Japan	Bark	Tumors	Abd and Mohamad, (2010)
	Seed	Laxative, purgative, hair fertilizer, and castor oil	
Hawaii			
	Sap	Scars and skin sores	Cesca *et al.* (2012)
Cook Islands	Seed	Stab wounds dressing	Hughes *et al.* (2019)
	Flower	Pus removal	
Pacific Islands	Seed	Infection, conjunctivitis, vaginal discharge, and skin problems	
	Bark	Skin inflammation	
	Flowers	Scalp care	
	Fruit	Abrasions on the scalp, toothaches, and corneal abrasions	
	Sap	Conjunctivitis and skin conditions	
	Leaf	Infections and swellings	
Brazil	Seed	Rheumatic diseases	Quintão *et al.* (2014)
	Leaf	Hepatitis, asthma, gastric ulcers, fever, headaches, and inflammation	Hoepers *et al.* (2015)
China	Bark	Sprue and thrush	González-Stuart and Rivera, (2019)
	Fruit	Fever, arthritis, skin ulcers, and headaches	
	Seed	Constipation and sciatic pain	
India	Seed	Ulcers	Lim, (2012)
Philippines	Seed	Purgative	

Cytotoxic activity

Even though the phrase "cytotoxic drug" lacks a valid meaning on a national or international level, knowledge of cytotoxicity has increased as awareness for molecular mechanisms has grown. Since various cytotoxic agents currently have significant limits, faults, and adverse effects, traditional herbal medicine becomes a steppingstone for drug research (Naghibi *et al.*, 2014). In this case, plant extracts are critical as a medicinal agent because they provide diverse compounds with various chemical structures and biological activities.

Toxicology studies revealed that the seed extract of *A. moluccana* 5,000 g/ml inhibits cell development by 35.18%, 37.18%, and 40.95% for the HeLa, SiHa, and VERO cells, respectively, while the LD_{50} was larger than 2,000 mg/kg. At high doses and with prolonged usage, the extract also shows evidence of toxicity and fatality in Wistar rats (de Castilho *et al.*, 2021). According to a study of the toxicological effect of *A. moluccana* seed extracts upon predatory fish, *Heteropneustes fossilis*, the acetone, methanol, and ethyl alcohol extracts had LC_{50} values of 906.998, 1,018.185, and 1,274.335 ppm, respectively, which were categorized as medium to less toxic (Sultana *et al.*, 2020). The same study on the Cichlid fish Tilapia, *Oreochromis niloticus* (Linn.), revealed that acetone, methanol, ethyl alcohol, and aquadest extracts exhibited toxicity giving LC_{50} values of 161.911, 278.776, 748.393, and 1,512.716 ppm, respectively (Sultana *et al.*, 2021).

A brine shrimp lethality test showed that LC_{50} of ethyl acetate, *n*-hexane, ethanol, and water fractions from the *A.*

moluccana stem bark were 17,102, 35,74, 39,294, and 380,932 µg/ml, respectively. It is predicted that the metabolite responsible for the high toxicity in the ethyl acetate fraction was flavonoid (Windyaswari *et al*., 2015). The leaves extract demonstrated cytotoxicity against HT29 human colon adenocarcinoma with percent of control sulforhodamine B (SRB) absorbance of 94 ± 8 and 101 ± 2, respectively, as well as against NCI-H460 human large cell lung carcinoma with a percent of control SRB absorbance of 60 ± 31 and 104 ± 3, respectively (Monks *et al*., 2002).

In addition, flavonoids, polyphenols, and tannins obtained from the leaf of *A. moluccana* are drug substances in breast cancer treatment functioning for secretion of tumor necrosis factor, as an immunostimulant, and for apoptotic induction (Suparna *et al*., 2018). Compounds **5** and **8** from the twigs and leaves extracts of this species displayed cytotoxicity against *Raji* cells (with IC_{50} 7.60 and 4.24 µg/ml, respectively) (Liu *et al*., 2007), while compound **14** showed the same property on HepG2 cells (IC_{50} 9.31 µg/ml) (Liu *et al*., 2008). Substances **10** and **16** also displayed cytotoxicity elsewhere (Alimboyoguen *et al*., 2014; Prabowo *et al*., 2013).

Anti-inflammatory activity

A complex process, including a biological reaction to contentious matters, such as injured cells, irritants, and infections, as manifested in a sophisticated manner by the vascular tissues, is inflammation's definition (e Sá and Andrade, 2013). Anti-inflammatory activity is an injury reaction involving cells and exudates in irritated tissues that protect the body from further damage and destruction. This activity explains why certain herbs are traditionally used to treat inflammatory diseases, including migraines, arthritis, fever, and pain (Yuan *et al*., 2006). The methanol extract of dried leaves from *A. moluccana* exhibited anti-inflammatory and antipyretic properties. The volume of rat paw edema induced by carrageenan was prevented from increasing by pretreatment with 100–300 mg/kg of this extract. The peak impact was reached at the 300 mg/kg dose (Niazi *et al*., 2010).

The methanol extract of leaves from *A. moluccana* displayed inflammatory mechanical sensitization in diverse inductor agents, partly associated with compounds **2** and **3** with 70% ± 2% and 50% ± 5% inhibition, respectively, on carrageenan-induced hypernociceptive response. In addition, compound **3** inhibited CFA (Complete Freund's Adjuvant) and PGE2 (Prostaglandin E2) induced mechanical sensitization by 25% ± 3% and 94% ± 6%, respectively (Quintão *et al*., 2011). Meanwhile, *α*- and *β*-amyrenone, metabolites derived from the dichloromethane fraction of the leaf methanol extract, demonstrated anti-inflammatory activity in both chronic and acute processes by decreasing mechanical hypersensitivity (Quintão *et al*., 2014). Meanwhile, the purification of ethanol extract from the leaves gave *α*-amyrin and *β*-amyrin, which are popular anti-inflammatory agents (Meyre-Silva *et al*., 1998). Furthermore, compound **17** derived from the stem bark methanol extract of this tree was previously proven to possess anti-inflammatory properties in another work (Prabowo *et al*., 2013).

Antinociceptive activity

Pain is a distressing sensory and emotional sensation that is related to, or resembles, real or prospective tissue damage, resulting in significant health expenditures and societal economic disadvantages (Amorim *et al*., 2021). Nociceptive pain begins with the stimulation or sensitization of nociceptors in the periphery that transmit and receive harmful impulses. Then, it ends with the activation of multiple supraspinal targets that regulate nociception, leading the individual to experience pain (Hernández-Avalos *et al*., 2021). Preliminary evaluation of *A. moluccana* revealed that the hydroalcoholic extract from *A. moluccana* leaves displayed solid antinociceptive activity with a mean ID_{50} value of 9.5 mg/kg and a maximum inhibitory activity of 88% ± 4% (Meyre-Silva *et al*., 1997, 1998).

The standardized dried extract of the leaves displayed a distinct antinociceptive effect by reducing nociception in mice, attributed to the presence of compound **3** obtained from the ethyl acetate fraction (Quintão *et al*., 2011). In a different work, *α*- and *β*-amyrenone were proven to also participate in the antinociceptive action of the dry extract (Quintão *et al*., 2014). This activity was also shown by the hydroalcoholic extracts of the bark, which was partly associated with the appearance of a atraric acid and compounds **6** and **16** (de Souza *et al*., 2021). This activity presumably explains the well-known use of *A. moluccana* as the traditional medication for pain and headaches in local wisdom (Ovia *et al*., 2021).

Other activities

Interestingly, other activities were also further shown by *A. moluccana*, indicating its extensive potential use as a source of novel drug candidates. For instance, the methanol extracts displayed 100% inhibition against the pancreatic lipase, suggesting that this plant has a high capability as an antiobesity agent (Saad *et al*., 2017). In addition, 300 mg/kg of this extract exhibited lipid-lowering properties by reducing body weight and serum lipids of "triton-induced hypercholesterolaemia and hyperlipaemic diet" rats (Pedrosa *et al*., 2002). In a different work, *α*- and *β*-amyrenone significantly inhibited enzymes found in the carbohydrate and lipid absorption mechanism, which are helpful for chronic metabolic medication, by lowering 96.5% ± 0.52% of α-glucosidase at 1.6 g/ml as well as demonstrating lipase-inhibitory activity with IC_{50} 82.99% ± 1.51% at 100 µg/ml (Ferreira *et al*., 2017). Conversely, Ubeda *et al.* (2017) did not find comparable outcomes with the seeds. They discovered that consuming the seeds elevated several indicators linked to cardiovascular risk. Furthermore, compounds from this species also showed at least anticancer, antifilarial, antiproliferation, antioxidant, antipyretic, antiplatelet aggregation, antidiabetes, antithyroid, antioxidative, and antihyperglycemic properties elsewhere (Prabowo *et al*., 2013).

CONCLUSION

This review highlighted some selected important chemical and biological reports on *A. moluccana* to profile the potency of this species as a promising source of novel drug candidates. Various scientific discoveries describe the prevalent utilization of this plant in folk medication since ancient times as a part of local wisdom in numerous tribes around the globe. However, exploration of secondary metabolites could be extended by using diverse methods to isolate more compounds from *A. moluccana*. In addition, the limited pharmacological data indicate the lack of clinical assessment on the biological activities. Hence, this study emphasizes the considerable opportunity to conduct further investigation and development in the revitalization of this species as a source of novel drug candidates. This work also foregrounds that local wisdom could be a starting point in searching for potent modern medicine.

ACKNOWLEDGMENT

The authors would like to thank the Applied Research from the Ministry of Education and Culture of Indonesia (Grant no. 3949/UN18.L1/PP/2021) and acknowledge the Institute of Research and Community Service of the University of Mataram.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

Not applicable.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

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How to cite this article:
Hakim A, Jamaluddin J, Al Idrus SW, Jufri AW, Sari Ningsih BN. Ethnopharmacology, phytochemistry, and biological activity review of *Aleurites moluccana*. J Appl Pharm Sci, 2022; 12(04):170–178.

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