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Pharmacological Activities, Isolated Compounds, Toxicity, and Potential for New Drug Discovery from the Genus Leea

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ABSTRACT

The genus Leea is widely recognized as a valuable source of medicinal plants, and half of its species are traditionally used to treat various diseases. According to previous studies, it also has significant potential for yielding molecules that can serve as drugs or lead compounds in the discovery of pharmaceutical products. Therefore, this review aimed to identify research gaps in the development of plant-based medicines from the genus Leea. The procedures comprised extracting data from 108 articles, which explored plants from the genus Leea and were published from 1997 to 2022. The articles reviewed consisted of data on pharmacological activity, isolated compounds, and toxicity potential. The results showed that among the 36 species in the genus, *L. indica, L. macrophylla, L. asiatica, L. aequata, L. aculeata, L. guinensis, and L. rubra* were often used in traditional medicine, leading to their frequent exploration in previous reports. A total of 66 compounds had been isolated, with 46 being known to have pharmacological activity. In addition, the dominant pharmacological activities of these compounds included antioxidant, antimicrobial, anti-inflammatory, and anticancer properties. The acute toxicity test results showed that the extract of plants from the genus was often categorized as not toxic at a dose of up to 2 g/kg BW. Based on the various pharmacological activities of the isolates and extracts, as well as the low toxicity potential, the genus Leea has the potential to be explored for the development of new drugs.

Keywords: Genus Leea, Pharmacological activity, Toxicity

INTRODUCTION

History proves that plants have consistently shown their significance as medicinal sources for treating various diseases. Several reports have also shown that the majority of drugs in prevalent use today are derived from either plant isolates or derivative compounds. In addition, the slogan "Back to nature" has inspired the development of various herbal medicines. Various plant genera, including Leea, have also become the focus of recent studies aimed at discovering and developing new drugs.

Leea is one of 14 genera in the Vitaceae family, which is widely known as the medicinal plant genus. Several studies have reported that the genus consists of plant species widely used in traditional medicine. Various countries, including India, Bangladesh, and Madagascar are known to use these species for the treatment of different diseases. The significance of the genus Leea is evident through its position as the focus of different literature reviews, with 2 being published in 2021. In addition, studies in Bangladesh have extensively explored its traditional uses and pharmacological activities (Hossain *et al*., 2021). A review of articles on the genus was also simultaneously published in India on the distribution, phytochemistry, and pharmacological activity, specifically for species commonly used in the country (Nehru *et al*., 2021). This current literature review was carried out to complement and extend the insights provided by these studies. The results are expected to present data on all species of the genus Leea, delving into individual examination of species used in therapy, as well as their pharmacological activity, isolated compounds, and toxicity data. The comprehensive display of isolated compounds and their pharmacological activities are essential in the discovery of new drugs. The toxicity data is also an essential factor, as both single-molecule drugs and

herbal medicines, must fulfill the aspects of efficacy (pharmacological activity) and safety as proven through toxicity tests.

Plants of the genus Leea are typically found growing in the wild without requiring special cultivation need, but the increasing human land usage can cause extinction. Therefore, this review article aims to increase human awareness regarding the crucial need to conserve this genus as a source of new medicine discoveries. The results can also serve as a guide in developing further related studies, particularly those aimed at finding new single-compound drugs and herbal products.

METHODOLOGY

The review began with the tracing of data on all species of the genus Leea on www.theplantlist.org website. A literature search was then carried out for each species in the database on Science Direct, PubMed, and Google Scholar. Subsequently, all articles collected were screened through their titles and abstracts. The reviewed articles presented data on activity tests, compound isolation, pharmacological activity of the isolated compounds, and toxicity tests of plants from the genus Leea.

RESULTS AND DISCUSSION

Species and Pharmacological Activities

The Plant List website (www.theplantlist.org) stated that there were 199 species of the genus Leea. These names consisted of the accepted names and synonyms, but only 36 of them had been declared taken (Table I). In addition, 14 of these species had been published for medicinal purposes. *L. indica* and *L. macrophylla* were the most studied species, followed by *L. asiatica*, *L. aequata*, *L. aculeata*, *L. guinensis*, and *L. rubra* (Table I).

Leea indica (Burm F.) Merr

L. indica was a favorite species that was widely studied for the treatment of various diseases. India and Bangladesh were reported to be the leading countries in terms of publications related to this plant species, followed by Malaysia and Singapore. Furthermore, this data was based on the number of articles found through online searches on the Google Scholar, PubMed, and Science Direct databases. Among the 16 publications reviewed in this section, 7, 4, 3, and 2 originated from India, Bangladesh, Malaysia, and Singapore, respectively.

Plant was often used in the traditional medicine of the people of Malaysia, India, Thailand, and China. The roots and leaves were traditionally used in the treatment of cancer, diabetes, diarrhea, dysentery, spasms, and various skin problems (Reddy *et al*., 2012). Several reports had shown that it possessed antioxidant and cytotoxic properties (Ghagane *et al*., 2017) (Rahman *et al*., 2013) and played a role in inhibiting the growth of various cancer cell lines (Wong *et al*., 2012) and inducing mitochondria-mediated apoptosis in cervical cancer (Wong & Abdul Kadir, 2012). Other studies also showed that it had antiproliferative (Siew *et al*., 2019), thrombolytic (Rahman, *et al*., 2013), antimicrobial (Rahman, *et al*., 2013), anticancer prostate (Ghagane *et al*., 2017), sedative (Raihan *et al*., 2011), and anxiolytic properties (Raihan *et al*., 2011).

In a study conducted by Hsiung (2011), 2 anticancer compounds were isolated, including mollic acid arabinoside and mollic acid xyloside, which belonged to the triterpenoid glycosides group. These compounds could inhibit the growth of Ca Ski cervical cancer cells, each with an IC_{50} value of 19.21 and 33.33 μM. According to previous reports, these compounds had not been previously identified in *L. indica* or any other species (Wong *et al*., 2012). In 2008, a total of 23 compounds were isolated from the plant (Table II).

Leea macrophylla Roxb. ex Hornem

Lee macrophylla was an edible wild plant, that was rich in minerals and vitamins (B1, B2, B12, and C), and could easily be found in South and Southeast Asian Regions, including India, Nepal, Bangladesh, Bhutan, Myanmar, Thailand, Cambodia, and Laos (Joshi *et al*., 2016). The plant's root had been the focus of several extensive studies, and it was often used in traditional medicine for the treatment of various conditions, such as goiter, colon cancer, lipoma, and tetanus (Mawa *et al*., 2019). Traditionally, the plant was considered effective in treating guinea worm and ringworm, as well as for healing wounds (Joshi *et al*., 2016).

This species was not only used empirically in therapy but had also been studied scientifically in several reports. Methanol extract of *L. macrophylla* roots had also been proven to have analgesic and anti-inflammatory activities. Doses of 100 and 200 mg/kg BW of this extract inhibited the formation of edema in carrageenan-induced animal models.

Table I. Accepted names species of the genus Leea and its synonym

Accepted Names	Synonym
L. aculeata Blume ex Spreng	*L. aculeata* var. moluccana Miq., *L. sandakanensis* Ridl., *L. serrulate* Miq., Ticorea aculeata Blanco
L. acuminatissima Merr.	-
L. aequata L.	*L. ancolona* Miq., *L. hirsuta* Blume ex Spreng, *L. hirta* Roxb. ex Hornem, *L. hispida* Gagnep, *L. kurzii* C.B Clarke
L alata Edgew.	-
L. *amabilis* Veitch ex Mast.	*L anambilis* var splendens Linden & Rodigas
L. angulata Korth. Ex Miq.	*L. horida* T. & B., *L. sambucina* var. intermedia Ridl.
L. asiatica (L.) Ridsdale	*L. crispa* L., *L. edgeworthii* Santapau, *L. herbacea* Buch.- Ham, *L. pinata* Andrews, *L. pumila* Kurz, Phytolaca asiatica L.
L. compactiflora Kurz	*L. bracteate* C.B Clarke, *L. trifoliata* M.A Lawson
L. congesta Elmer	*L. capitata* Merr.
L. coryphantha Lauterb.	-
L. curtisii King	*L stipulosa* Gagnep.
L. glabra C.L. Li	-
L. gonioptera Lauterb.	-
L. grandifolia Kurz	-
L. guineense G. Don	*L. coccinea* Bojer
L. guineensis G. Don	*L. acuminata* Wallich ex Clarke, *L. arborea* Sieber ex Bojer, *L. arborea* Telf. Ex Wight & Arn., *L. aurantiaca* Zoll. & Moritzi, *L. bopinnata* Boivin, *L. bulusanensis* Elmer, *L. cochinea* Planch, etc
L. indica (Burm. F.) Merr.	*Aquilicia otillis* Gaerth, *L. biserrata* Miq., *L. gigantea* Griff, *L. otillis* (Gaerthn.) DC., *L. ramosii* Merr, etc
L. krukoffiana Ridsdale.	-
L. longifolia Merr	-
L. macrophylla Roxb. ex Hornem	*L. angustifolia* P. Lawson, *L. aspera* Wall. Ex G. Don., *L. diffusa* P. Lawson, *L. latifolia* Wall. Ex Kurz., *L. robusta* Roxb., etc
L. Macropus K. Schum. & Lauterb.	-
L. Magnifolia Merr.	*L. banahaensis* Elmer, *L. catanduanensis* Quisumb., *L. picnanta* Quisumb. & Merr.
L. papuana Merr. & L.M Perry	-
L. philippinensis Merr	*L. nitida* Merr., *L. philippinensis* var. pauciflora Merr.
L. quadrifida Merr.	*L. agusanensis* Elmer, *L. platiphylla* Merr.
L. rubra Blume ex Spreng	*L. brunoninan* C.B Clarke, *L. linearifolia* C.B Clarke, *L. polyphylla* Miq., *L. rubra* var. apiifolia Zipp. Ex Miq., *L. rubra* f. celebica Koord., *L. rubra* var polyphylla (Miq.) Miq.
L. saxatilis Ridl.	-
L. setuligera C.B Clarke	*L. mastersii* C.B Clarke, *L. mastersii* var. siamensis W.G Craib., *L. tenuifolia* W.G Craib.
L. simplicifolia Zoll. & Moritzi	*L. forbesii* Baker f., *L. pauciflira* King, *L. pauciflora* var. ferruginea W,G Craib
L. smithii Koord.	-
L. spinea Desc.	-
L. tetramera Burtt	*L. solomonensis* Merr. & L.M Perry, *L. suaveolens* Merr. & L.M Perry
L. thorelii Gagnep.	*L. tetrasperma* Gagnep
L. tinctorial Baker	-
L. unifoliate Merr.	*L. longiopetilata* Merr.
L. zippeliana Miq.	*L. micholitzii* Sanders, *L. monophyla* Lauterb, *L. zippeliana* var. ornate Lauterb

Table II. Compounds that have been isolated from the genus Leea and the pharmacological activity of each compound

Compound name	Species	Pharmacological Activity
	Triterpenoid	
4-hydrophenol-β-D-{6-O-[4-O(7S,8R-guaiacylglycerol-8-yl)-3-methoxybenzoyl]}-β-D-glucopyranoside **(1)**	*L. asiatica* (Kil *et al*., 2019)	-
Oleanolic acid **(2)**	*L. asiatica* (Kil *et al*., 2019) *L. macrophylla* (Mahmud *et al*., 2017) *L. indica* (D. Singh *et al*., 2019)	Anticancer (Liese *et al*., 2015), antidiabetic (Su *et al*., 2010), antimicrobial (Wang *et* 2015)(Jesus *et al*., 2015), hepatoprotect (Gutiérrez-Rebolledo *et al*., 201 antihypertensive (Bachhav *et al*., 2011), a inflammatory (Lee *et al*., 2013), antiparas (Sifaoui *et al*., 2017)
7α,28-olean diol **(3)**	*L. macrophylla* (Mahmud *et al*., 2017)	-
Stigmasterol **(4)**	*L. macrophylla* (Mahmud *et al*., 2017), *L. thorelii* (Lakornwong *et al*., 2014)	Antioxidant and neuroprotective (Pratiwi *et* 2021), antidiabetic (Wang *et al*., 201 antimicrobial (Alawode *et al*., 2021)
Ursolic acid **(5)**	*L. asiatica* (Kil *et al*., 2019)	Antibacterial (Jesus *et al*., 2015)(Do Nascime *et al*., 2014) (Qian, Wang, *et al*., 202 antioxidant (Do Nascimento *et al*., 2014), a inflammatory (Checker *et al*., 2012), antican (Khwaza *et al*., 2020)
Maslinic acid **(6)**	*L. asiatica* (Kil *et al*., 2019)	Antimicrobial (Sifaoui *et al*., 2017), antioxid (Mokhtari *et al*., 2015), antitumor (Fuentes-R *et al*., 2022), antidiabetic (Cui *et al*., 2015)
Chebuloside II **(7)**	*L. asiatica* (Kil *et al*., 2019)	Anti-inflammatory (Yang *et al*., 2014)
Corosolic acid **(8)**	*L. asiatica* (Kil *et al*., 2019)	Antidiabetic and antihyperlipidemic (Xu *et* 2019), antitumor (Ma *et al*., 2018), a inflammatory (Kim *et al*., 2016)
Hederagenin-3-O-arabinopyranoside **(9)**	*L. asiatica* (Kil *et al*., 2019)	Anticancer (Li *et al*., 2015)
Oleanolic acid 3-O-glucopyranosyl-(1->2)-arabinopyranoside **(10)**	*L. asiatica* (Kil *et al*., 2019)	-
	Flavonoid	
(+)-catechin **(11)**	*L. asiatica* (Kil *et al*., 2019) *L. thorelii* (Kaewkrud *et al*., 2007)	Antioxidant (Bernatoniene & Kopustinskie 2018), antibacterial (Gopal *et al*., 2016)
(-)-epicatechin **(12)**	*L. asiatica* (Kil *et al*., 2019) *L. thorelii* (Kaewkrud *et al*., 2007)(Lakornwong *et al*., 2014)	Antibacterial (Gopal *et al*., 2016)
(-)-epicatechin gallate **(13)**	*L. thorelii* (Lakornwong *et al*., 2014)	Antibacterial (Gopal *et al*., 2016)
4”-O-methyl-(-)-epicatechin gallate **(14)**	*L. thorelii* (Lakornwong *et al*., 2014)	-
(-)-epiafzelechin **(15)**	*L. asiatica* (Kil *et al*., 2019)	Protects against estrogen deficiency-indu bone loss (Wong *et al*., 2017)
Juglanin **(16)**	*L. asiatica* (Kil *et al*., 2019)	Anti-inflammatory and protection against L triggered acute lung injury (Dong & Yuan, 20

Table II Continue.

Compound name	Species	Pharmacological Activity
	Flavonoid	
Mearnsetin 3-O-rhamnopyranoside **(17)**	*L. asiatica* (Kil *et al*., 2019)	-
Myricitrin **(18)**	*L. asiatica* (Kil *et al*., 2019) *L. thorelii* (Kaewkrud *et al*., 2007)	Antioxidant, anti-inflammatory, antifibrotic a hepatoprotective (Domitrović *et al*., 2015)
Afzelin **(19)**	*L. asiatica* (Kil *et al*., 2019)	Anticancer, antibacterial (Zhu *et al*., 2015)
Quercitrin **(20)**	*L. asiatica* (Kil *et al*., 2019) *L. indica* (D. Singh *et al*., 2019) *L. thorelii* (Kaewkrud *et al*., 2007)	Antioxidant, antimicrobial, antiprotozoal, a anti-inflammatory (El-Saber Batiha *et al*., 202
Quercitrin-3'-sulphate **(21)**	*L. guineense* (De Beck *et al*., 2003)	Antioxidants (De Beck *et al*., 2003)
Quercitrin-3,3'-disulphate **(22)**	*L. guineense* (De Beck *et al*., 2003)	Antioxidants (De Beck *et al*., 2003)
Quercitrin-3,3',4'-trisulphate **(23)**	*L. guineense* (De Beck *et al*., 2003)	Antioxidants (De Beck *et al*., 2003)
Astragalin **(24)**	*L. aequata* (Tun *et al*., 2019)	Anti-inflammatory (Walker *et al*., 201 antioxidant (Riaz *et al*., 2018)
Isorhamnetin-3-O-β-D-glucopyranoside **(25)**	*L. aequata* (Tun *et al*., 2019)	Antiadipogenic (antiobesity) (Kong & Seo, 20
Isoquercitrin **(26)**	*L. aequata* (Tun *et al*., 2019)	Antioxidant, anti-inflammatory, xanth oxidase inhibitor (Valentová *et al*., 2014)
Mauritianin **(27)**	*L. aequata* (Tun *et al*., 2019)	Antioxidants (Kicel & Wolbiś, 2012)
Mearnsitrine **(28)**	*L. rubra* (N. Das *et al*., 2022)	Prevents DNA damage, anticancer (N. Das *et* 2022)
	Coumarin	
Microminutinin **(29)**	*L. thorelii* (Lakornwong *et al*., 2014)	Antihyperglycemic, antihyperlipider antiapoptotic (MM Koriem *et al*., 2013)
5-hydroxymethylfurfural **(30)**	*L. aequata* (Tun *et al*., 2019)	Antifungals (Lemos *et al*., 2020)
Scopoletin **(31)**	*L. aequata* (Tun *et al*., 2019)	Antioxidant, cancer chemoprevention (Zhac *al*., 2013)
	Phenolic glycosides	
Breynioside **(32)**	*L. asiatica* (Kil *et al*., 2019)	Antioxidants (Ammari *et al*., 2021)
7-O-methylmearnsitrin **(33)**	*L. aequata* (Rahim *et al*., 2021)	Antiproliferative (anticancer) (Rahim *et* 2021)
Roseoside A ((6S,9R)-roseoside) **(34)**	*L. aequata*(Tun *et al*., 2019) (Rahim *et al*., 2021)	Antiproliferative (anticancer) (Rahim *et* 2021), antihypertensive (Hong *et al*., 2019), a inflammatory, antiallergic, protease inhibi COVID-19 (Ebada *et al*., 2020)
(6S,9S)-roseoside C **(35)**	*L. aequata* (Tun *et al*., 2019)	-
	Diglycosidic compounds	
Phenylethyl-rutinoside **(36)**	*L. asiatica* (Kil *et al*., 2019)	-
Icariside D1 **(37)**	*L. asiatica* (Kil *et al*., 2019)	-
Hexenyl-rutinoside **(38)**	*L. asiatica* (Kil *et al*., 2019)	-
Everlastoside C **(39)**	*L. asiatica* (Kil *et al*., 2019)	-
	Miscellaneous compound	
Bergenin **(40)**	*L. asiatica* (Kil *et al*., 2019) *L. indica* (D. Singh *et al*., 2019) *L. thorelii* (Lakornwong *et al*., 2014)	Antioxidant, antiplasmodial (H. Khan *et* 2016)

Table II Continue

Compound name	Species	Pharmacological Activity
	Miscellaneous compound	
11-O-acetyl bergenin **(41)**	*L. thorelii* (Lakornwong *et al*., 2014)	Antitrypanosomal (Nyunt *et al*., 2012)
11-O-(4'-methylgalloyl) bergenin **(42)**	*L. thorelii* (Lakornwong *et al*., 2014)	Antioxidant, anti-inflammatory, and antiarthr (El-Hawary *et al*., 2016)
Citroside A **(43)**	*L. asiatica* (Kil *et al*., 2019) *L. thorelii* (Kaewkrud *et al*., 2007)	Anti-inflammatory (Guo *et al*., 2021)
Gallic acid **(44)**	*L. indica* (D. Singh *et al*., 2019)	Antimicrobial, anticancer, gastrointesti protective, and cardioprotective (Kahkeshan *al*., 2019)
3,5-dihydroxy-4-methoxy benzoic acid **(45)**	*L. thorelii* (Lakornwong *et al*., 2014)	-
Methyl gallate **(46)**	*L. indica* (D. Singh *et al*., 2019)	Antioxidants (Ekaprasada *et al*., 2010)
Epigallocatechin-3-O-gallate **(47)**	*L. indica* (D. Singh *et al*., 2019)	Antiviral (Kaihatsu *et al*., 2018), a inflammatory, antidiabetic, antiobes antitumor (Min & Kwon, 2014)
Myricetin-3-O-rhamnoside **(48)**	*L. indica* (D. Singh *et al*., 2019)	Accelerate wound healing, anti-inflammat (Elloumi *et al*., 2022), antibacterial (Motlhatl *et al*., 2020), hepatoprotective (Domitrović *et* 2015)
Quercetin-3-O-rhamnoside **(49)**	*L. indica* (D. Singh *et al*., 2019)	Accelerate wound healing, anti-inflammat (Elloumi *et al*., 2022), α-glucosidase inhibit (anti-diabetics) (Utari *et al*., 2019)
Mollic acid arabinoside **(50)**	*L. indica* (Y. H. Wong *et al*., 2012)	Anticancer (Y. H. Wong & Abdul Kadir, 2012)
Mollic acid xyloside **(51)**	*L. indica* (Y. H. Wong *et al*., 2012)	Anticancer (Y. H. Wong & Abdul Kadir, 2012)
	Neolignan	
(7S,8R)-9'-O-acetylcedrusin **(52)**	*L. aequata* (Tun *et al*., 2019)	-
	Lactam	
(3S,4S)-4-chloro-3-hydroxypiperidin-2-one **(53)**	*L. aequata* (Tun *et al*., 2019)	-
	Lignan	
9-O-acetylisolariciresinol **(54)**	*L. aequata* (Tun *et al*., 2019)	-
(+)-lariciresinol **(55)**	*L. aequata* (Tun *et al*., 2019)	Antifungal (Hwang *et al*., 2011)
(+)-syringaresinol **(56)**	*L. aequata* (Tun *et al*., 2019)	Anti-inflammatory (Xu *et al*., 2019)
Urolignoside **(57)**	*L. aequata* (Tun *et al*., 2019)	-
	Others	
Trans-N-p-coumaroyltyramine **(58)**	*L. aequata* (Tun *et al*., 2019)	A-glucosidase inhibitors (anti-diabeti (Nishioka *et al*., 1997)
N-trans-feruloyltyramine **(59)**	*L. aequata* (Tun *et al*., 2019)	Antioxidant, anti-inflammatory (SaeYoon *et* 2015)
Vanillic acid **(60)**	*L. aequata* (Tun *et al*., 2019)	Antibacterial (Qian, Fu, *et al*., 2020)
Syringic acid **(61)**	*L. aequata* (Tun *et al*., 2019)	Antioxidants (Cikman *et al*., 2015)
α-hydroxyacetovanillone **(62)**	*L. aequata* (Tun *et al*., 2019)	
3,4,5-trihyroxybenzoic acid ethyl ester **(63)**	*L. aequata* (Tun *et al*., 2019)	-
dihydro-p-methoxy cinnamic acid **(64)**	*L. aequata* (Tun *et al*., 2019)	-
Isotachioside **(65)**	*L. aequata* (Tun *et al*., 2019)	-

In addition, the extract showed analgesic activity starting at a dose of 50 mg/kg BW (Hossain *et al*., 2020). N-hexane, chloroform, ethyl acetate, and methanol extracts of *L. macrophylla* seeds effectively inhibited the growth of gram-positive bacteria and yeast (*Candida albicans*) (Islam *et al*., 2013).

The antioxidant activity of this plant had also been proven by several studies. According to Islam, extracts from various *L. macrophylla* seeds exhibited significant antioxidant properties by scavenging free radicals, such as DPPH, superoxide, and NO. This activity could be attributed to compounds, such as oleanolic acid and its derivatives, as well as stigmasterol, which played essential roles in these effects (Islam *et al*., 2013). Further studies proved that the seed extract had hepatoprotective (Akhter *et al*., 2015) and neuroprotective activities (Ferdousy *et al*., 2017), as well as antidiabetic through its protective effect on pancreatic β cells (Mawa *et al*., 2019).

The methanol extract of *L. macrophylla* leaves was shown to have the ability to repair damage to the liver tissue of albino Wistar rats induced using CCl_4. In addition, CCl_4-induced mice showed increased serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Treatment with the plant's ethanol extract caused a decrease in the serum levels of these 3 enzymes (Akhter *et al*., 2015). This study carried out a series of field tests, hole cross tests, EPM, and thiopental sodium-induced tests. Albino Wistar rats were used in the trial, and open field and hole cross-tests were carried out to assess the locomotor activity of the animals, while EPM was used to evaluate anxiolytic effects. A decrease in locomotor activity indicated a sedative effect (Ferdousy *et al*., 2017), and the results showed that the extract had central nervous system depressant, anxiolytic, and sedative activity (Ferdousy *et al*., 2017).

Mawa (2019) proved that *L. macrophylla* root extract could stimulate the performance of the pancreas. Test animals treated with this plant root extract for 3 weeks showed improvement in pancreatic β cells. The results of this study were an early indication of its use as a functional food source for people with type 2 diabetes mellitus (Mawa *et al*., 2019).

***Leea aequata* L.**

Compared to *L. macrophylla*, *L. aequata* was widely distributed in mainland south and southeast Asia. This shrub was one of the plants used in traditional medicine in Myanmar, and its fresh leaves were typically ground for wound treatment (Tun *et al*., 2019). In addition, the people of Tanah Karo, Indonesia, used them for wound care and as muscle relaxants for tetanus sufferers (Ginting *et al*., 2018). The seeds, roots, and bark had also showed antimicrobial activity (Tun *et al*., 2019) (Kujur, 2010).

In a previous study, 23 compounds were successfully isolated from the ethanol extract of the plant's aerial part. Among these, 3,4,5-trihydroxybenzoic acid ethyl ester showed antibacterial activity (Tun *et al*., 2019). Furthermore, its leaves were found to possess antioxidant and antiproliferative properties (Hossain *et al*., 2021), and this finding was consistent with further reports. A total of compounds from *L. aequata* leaves, namely 7-O-methylmearnsitrin and roseoside A, had inhibitory effects on HeLa cell proliferation, showing their potential as anticancer agents (Rahim *et al*., 2021).

***Leea asiatica* (L.) Ridsdale**

The fruit of the *L. asiatica* plant was usually consumed by people in the northwest Himalayas, India (Singh *et al*., 2015), and was used to treat various diseases. The Karnataka tribe used this plant for the treatment of fractures, while inhabitants of the Andaman Islands used the roots to treat boils and wounds. Several studies showed that the Tripura tribe used the leaves to treat worm infections and liver diseases. This plant had also been used in several other areas for eye pain, diabetes, and gastrointestinal disorders (Sen *et al*., 2013).

The usage of this plant for medicine had motivated experts to study and confirm their ideas. The methanol extract of *L. asiatica* leaves was found to be effective against worm infections and exhibited antioxidant properties (Sen *et al*., 2012). Furthermore, it also had neuroprotective activity (Sen *et al*., 2013), hepatoprotective (Sen *et al*., 2014), anti-inflammatory, and accelerated wound healing. Compared to the leaves, the fruit also had good potential to be studied in more depth due to its rich polyphenol content, which could effectively capture free radicals. The ability of various compounds to inhibit enzyme activity, which led to skin aging and skin darkening, made the fruit worthy of consideration as an ingredient in making cosmetics (Singh *et al*., 2015).

More in-depth studies had been carried out by isolating compounds from this plant. Kil *et al*. (2019) separated the methanol extract of the aerial part, leading to the isolation of 24 compounds. In

addition, one of them was a new phenolic glucoside, namely: 4-hydrophenol-β-D-{6-O-[4-O(7S,8R-guaiacylglycerol-8-yl)-3-methoxybenzoyl]}-β-D-glucopyranoside (Kil *et al*., 2019).

Leea rubra

Leea rubra was known as the red tree shrub, which could easily be found wild in forests on the continents of Asia and Australia (Das *et al*., 2022). The Lanna indigenous people in Thailand had traditionally used the roots and bark to treat gastrointestinal diseases (Kadchumsang *et al*., 2014), while it was commonly used to treat hypertension in Brazil (Braga *et al*., 2007).

Scientific evidence efforts showed that *L. rubra* had several pharmacological activities, including antioxidant, anticancer, and antibacterial (Das *et al*., 2021) (Kadchumsang *et al*., 2014). The results of other studies showed that this plant also had the potential to be developed as a functional food source. This was primarily attributed to the content of essential amino acids and minerals necessary for health (Awotedu *et al*., 2018) (Ajiboye *et al*., 2014).

Leea guineensis

Residents of Ghana often used *Leea guineensis* to treat various diseases, including epilepsy and pain (Woode *et al*., 2011). Other uses included the treatment of toothache, gonorrhea, detection of pregnancy, various skin problems, diarrhea, dysentery, indigestion, herpes, and ulcers (Ajiboye *et al*., 2014). In addition, scientific research showed that it had potential as a medicinal plant due to its antinociceptive, anxiolytic, anticonvulsant (Woode *et al*., 2011), anti-inflammatory (Falodun *et al*., 2007), and hepatoprotective properties (Ajiboye *et al*., 2014).

Leea aculeata

Leea aculeata was often used in traditional medicine and was easy to find in low to moderate plains in forests along rivers. Furthermore, it was a shrub plant (Gonzales *et al*., 2019), which had traditionally been used as an antipyretic, postpartum care, poultice, and for the treatment of headaches (Villazorda, 2015). Scientific studies proved that it had antioxidant (Villazorda, 2015) and anti-hyperuricemia activity by inhibiting xanthine oxidase enzyme activity (Gonzales *et al*., 2019).

Leea alata

Leea alata was a medicinal plant, and its root was commonly used in the treatment of jaundice by the indigenous people of Korku, India (Choudhary and Upadhyaym, 2012).

Leea thorelii

Leea thorelii was a small shrub that grew wild and had traditionally been used by Thai people as an antipyretic and anti-inflammatory agent (Kaewkrud *et al*., 2007). Kaewkrud *et al*. (2007) had successfully isolated 5 compounds from its leaves, such as citroside, a megastigmane that had not been reported from any other species, while the structure of the other 4 compounds had not yet been determined (Kaewkrud *et al*., 2007). Lakornwong *et al*. (2014) successfully isolated 8 compounds from its roots, including bergenin and 2 of its derivatives, a gallic acid derivative, 3 flavan compounds, and a coumarin (Table II) (Lakornwong *et al*., 2014).

Leea angulata

The people of the Sasak tribe in Lombok, Indonesia, usually used the bark of *L. angulata* plant for wound healing. The community stated that the use of its bark could reduce pain and improve wound healing (Hidayah & Barlian, 2022). Furthermore, Hidayah *et al*. (2021) proved that the plant bark extract could accelerate the proliferation process, thereby accelerating wound healing (Hidayah & Barlian, 2022).

Leea guineense

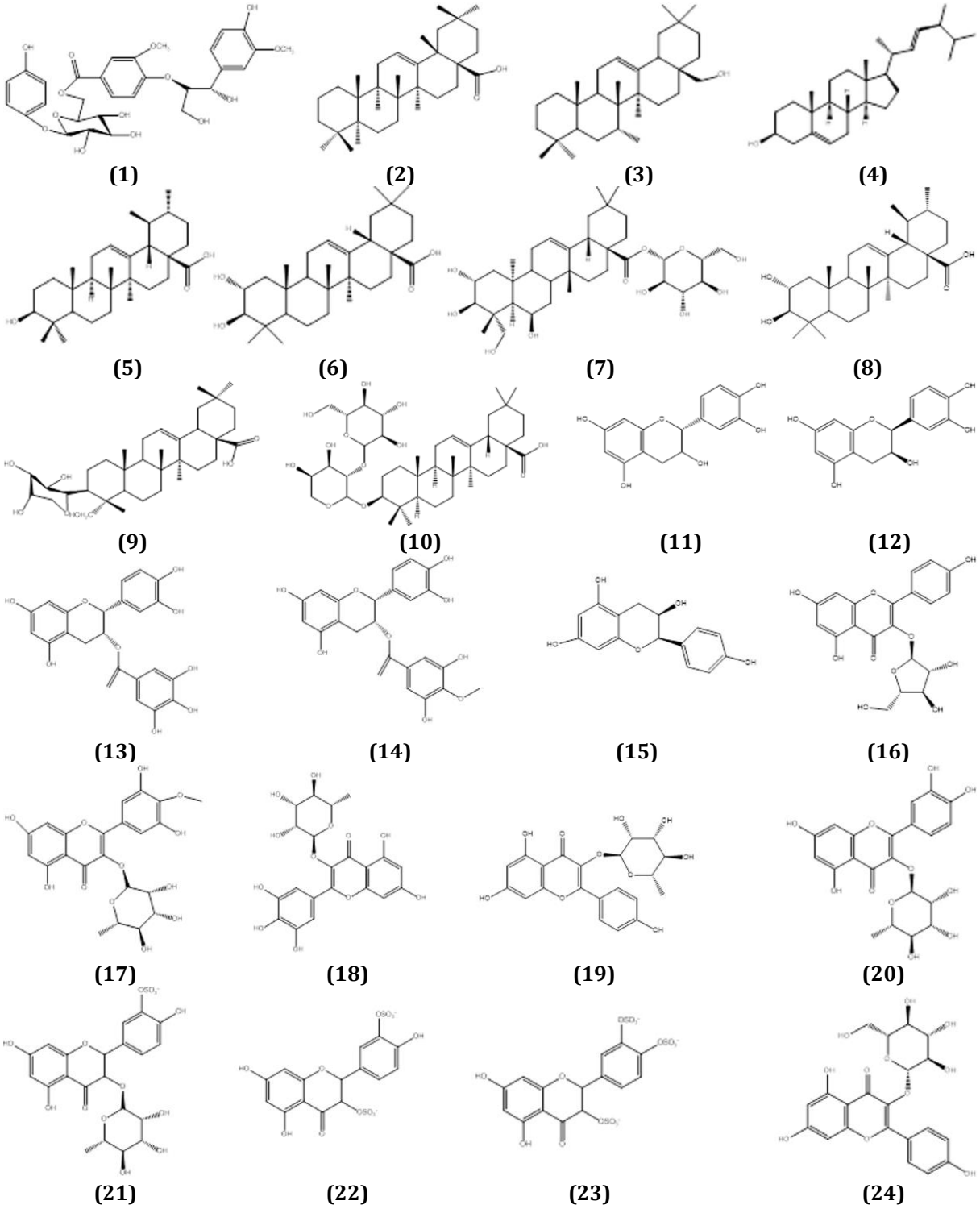
Leea guineense was traditionally used as an anti-inflammatory agent due to its composition of essential compounds (De Beck *et al*., 2003). De Beck *et al*. 1999 successfully isolated a flavonoid, namely quercitrin-3'-sulphate from the plant, while 2 other quercitrin sulphate compounds were identified in 2003 and their antioxidant activity was tested. In addition, the 2 new compounds were quercitrin 3,3'-disulphate and quercitrin 3,3',4'-trisulphate (De Beck *et al*., 2003). Studies on this plant ended in 2003, as evidenced by the absence of publications regarding its potential as a medicinal plant.

Leea philipinensis

Leea philipinensis was an endemic plant in the Philippines, and there were no reports on its empirical use for treatment. However, a previous study proved this plant had antioxidant activity due to its beneficial composition (Santiago & Bartolome, 2015).

Leea tetramera

Based on previous reports, there were no publications on the use *of Leea tetramera* in traditional medicine. Khan *et al*. proved that the plant extract could inhibit the growth of various bacteria (Khan *et al*., 2003), but after 2003, there were no more publications on its potential for treatment.



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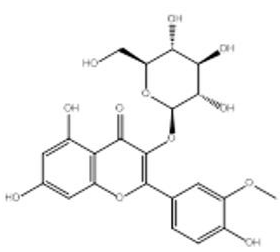

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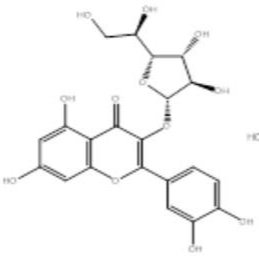

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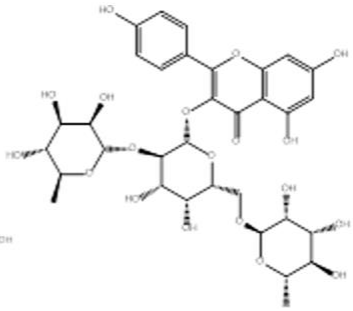

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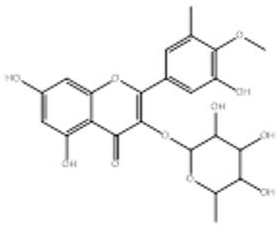

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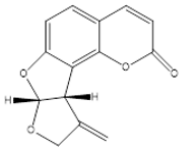

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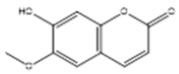

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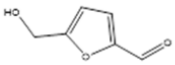

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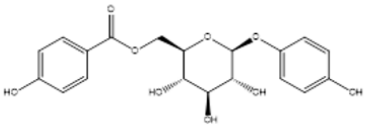

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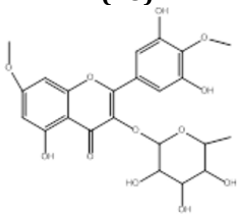

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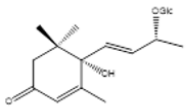

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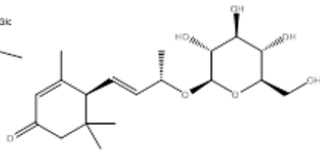

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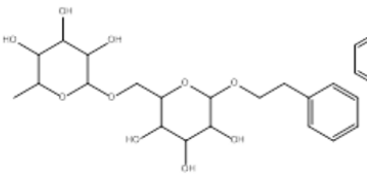

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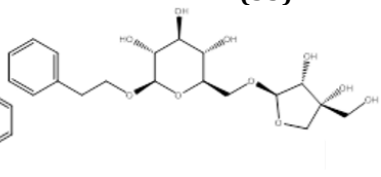

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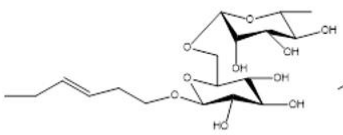

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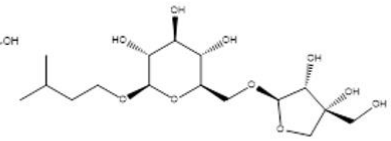

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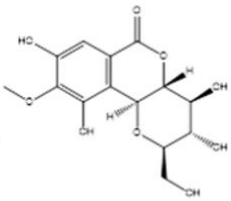

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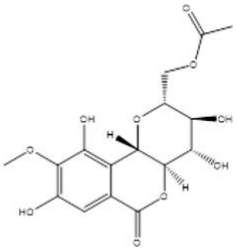

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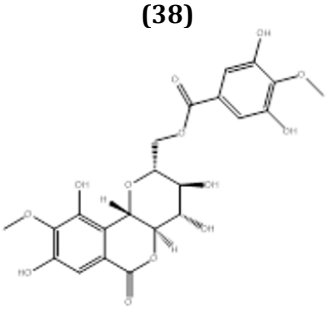

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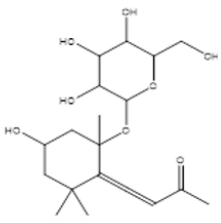

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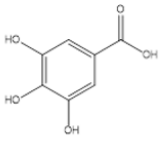

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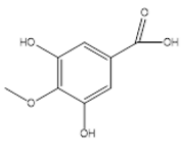

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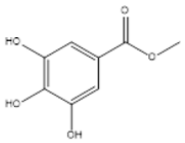

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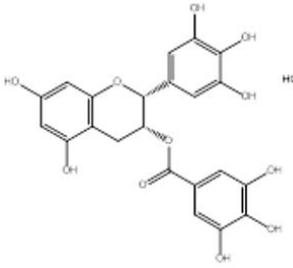

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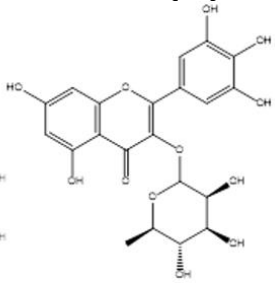

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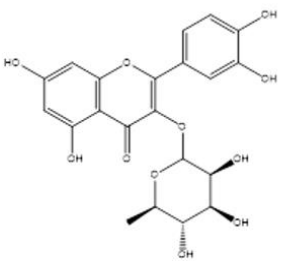

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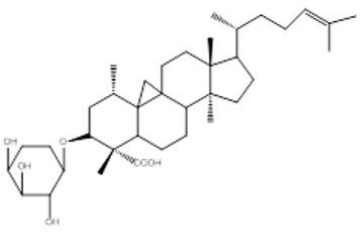

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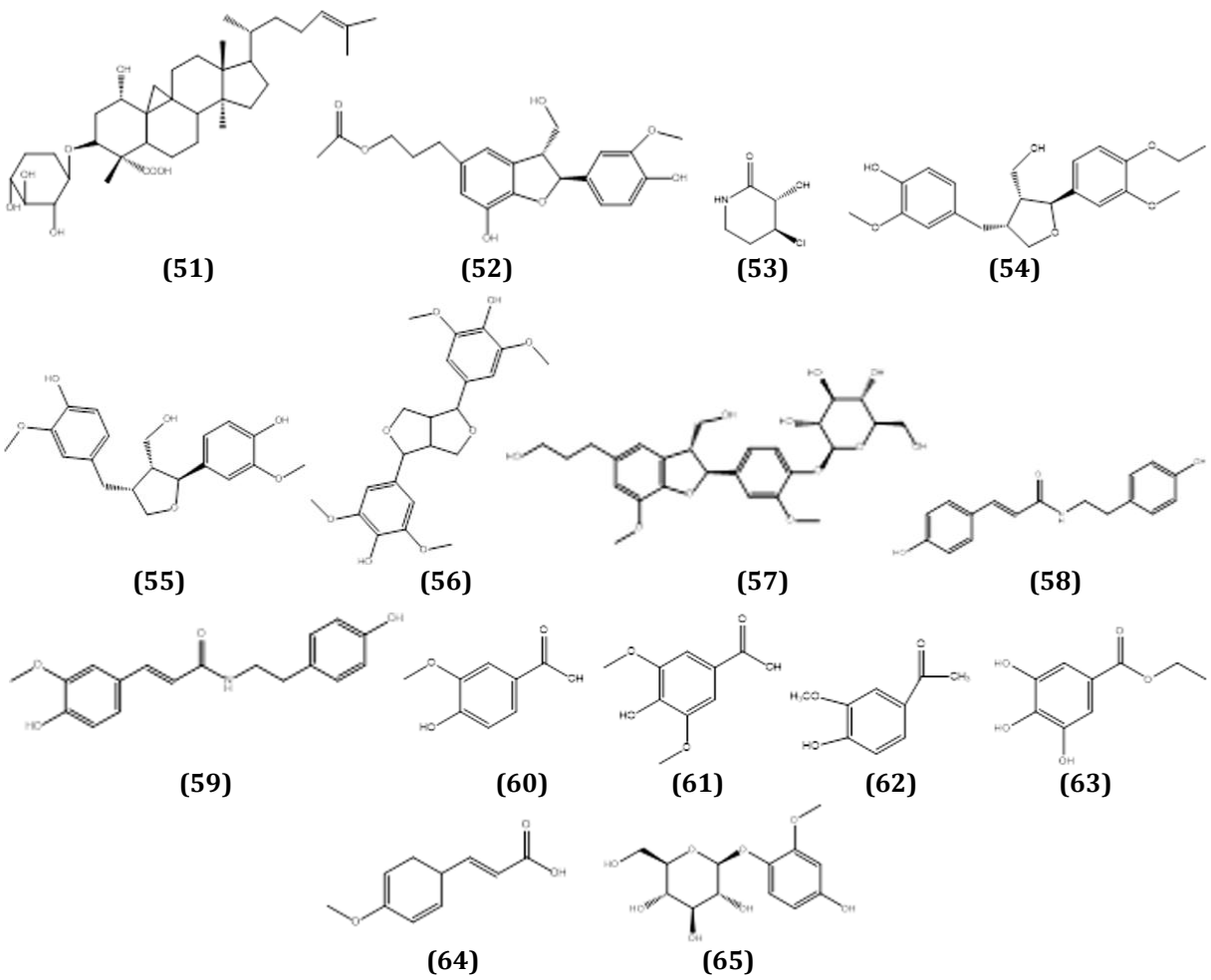

Figure 1. The structure of the isolated molecules from the genus Leea

Isolated Compounds

Several species of this genus had provided an increased vocabulary of potential chemical compounds to be developed as drugs, food additives, and others. *L. indica*, *L. macrophylla*, L. *asiatica*, and *L. aequata* were the prototype plants of this genus, which had been intensely studied for the isolation of constituent compounds. Several isolates of these compounds had also been tested for their activities (Table II).

Toxicity

Toxicity tests of plants from the genus Leea were generally still limited to acute oral toxicity tests and were often declared safe. Based on findings, no death cases had been reported during acute toxicity test, and observations of vital organs (heart, liver, kidneys, lungs, and brain) showed no toxicity signs (Table III).

CONCLUSION

In conclusion, *L. macrophylla*, *L. indica*, and *L. aequata* were species of the genus Leea, which had been extensively explored. These plants were used in traditional medicine and had been tested for their activity, toxicity, and phytochemical content. In addition, their acute oral toxicity test showed a low toxicity potential, while the activity test showed promising pharmacological properties. Based on these findings, the plants had the potential to be developed into medicine. Phytochemistry study also found that some compounds had pharmacological activity as a single compound, and could be developed into new drugs or lead compounds to discover new drug molecules.

CONFLICT OF INTEREST

All authors declare that they do not have any conflicts of interest.

Table III. Toxicity test on several Leea species

Species	Tested part	Test result
L. indica	Leaves alcohol and hydroalcoholic extracts	Extracts are safe up to a dose of 3 g/Kg BW; no signs of toxicity were found (Dalu, D., Duggirala, S., & Akarapu, 2014)
L. macrophyla	Ethanol extracts all parts of the plant	There is no acute toxicity up to a concentration of 3.5 g/Kg BW (Nizami et al., 2012)
	Leaves methanol extract	No deaths were up to a dose of 2 g/Kg BW. In subacute toxicity, no signs of toxicity were found. There were no significant changes in body weight and the kidneys, liver, heart, and brain weight. These organs also did not show any histological changes. Biochemical and hematologic parameters were almost the same as control animals (Akhter et al., 2015)
	Root tuber ethanol extract	The safety limit of the extract is 5 g/Kg BW when administered orally. The section did not cause behavioral modulation, symptoms of toxicity, and morbidity. In acute dermal toxicity: the extract does not induce swelling, inflammation, irritation, or other skin abnormalities (Joshi et al., 2016)
L. rubra	One of the isolates, myricetin 4'-methoxy-3-Oα-L-rhamnopyranosid	In the research procedure, it was mentioned that there was a determination of LD_{50} in experimental rats, but the results section did not find this data (S. Das et al., 2022)
L. aequata	Leaves ethanolic extract	There were no deaths after administration of a single dose up to 2000 mg/Kg BW (Bulbul et al., 2022)
Other species	No toxicity test data found	

REFERENCES

A. Nehru, Y. Shah, J. Sharma, P. Thummar, P. Verma, M. S. (2021). A comprehensive review on the genus *Leea* (family Leeceae) with special emphasis on the Indian species. *International Journal of Pharmaceutical Sciences and Research, 12*(5), 2559–2569. https://doi.org/10.13040/IJPSR.0975-8232.12(5).2559-69

Ajiboye, B. O., Oso, A.., & Kobomoje, O. (2014). Chemical composition and nutritional evaluation of *Leea guineensis* seed. *International Journal of Food Science, Nutrition and Dietetics*, *3*(2), 94–98.

Akhter, S., Rahman, M. A., Aklima, J., Hasan, M. R., & Hasan Chowdhury, J. M. K. (2015). Antioxidative role of hatikana (*Leea macrophylla* Roxb.) partially improves the hepatic damage induced by CCl4 in Wistar Albino Rats. *BioMed Research International*, *2015*. https://doi.org/10.1155/2015/356729

Alawode, T. T., Lajide, L., Olaleye, M., & Owolabi, B. (2021). Stigmasterol and β-sitosterol: Antimicrobial compounds in the leaves of *Icacina trichantha* identified by GC–MS. *Beni-Suef University Journal of Basic and Applied Sciences*, *10*(1). https://doi.org/10.1186/s43088-021-00170-3

Ammari, N. A., Wahongan, G. J. P., & Bernadus, J. B. B. (2021). Uji potensi ekstrak daun pepaya (*Carica papaya* linn) sebagai larvasida terhadap larva *Aedes sp.* di Manado (The potential evaluation of papaya leaf extract (*Carica papaya* linn) as a larvicide against *Aedes sp* larvae. in Manado). *Jurnal E-Biomedik*, *9*(1), 1–8. https://doi.org/10.35790/ebm.v9i1.31733

Awotedu, O. L., Ogunbamowo, P. O., Emmanuel, I. B., & Lawal, I. O. (2018). Phytominerals and phytochemical studies of *Azadiracthta indica, Leea guineensis* and *Parkia biglobosa* leaves. *International Annals of Science*, *6*(1), 28–34. https://doi.org/10.21467/ias.6.1.28-34

Bachhav, S. S., Patil, S. D., Bhutada, M. S., & Surana,

S. J. (2011). Oleanolic acid prevents glucocorticoid-induced hypertension in rats. *Phytotherapy Research*, *25*(10), 1435–1439. https://doi.org/10.1002/ptr.3431

Bernatoniene, J., & Kopustinskiene, D. M. (2018). The role of catechins in cellular responses to oxidative stress. *Molecules*, *23*(4), 1–11. https://doi.org/10.3390/molecules23040965

Braga, F. C., Serra, C. P., Viana Júnior, N. S., Oliveira, A. B., Côrtes, S. F., & Lombardi, J. A. (2007). Angiotensin-converting enzyme inhibition by Brazilian plants. *Fitoterapia*, *78*(5), 353–358. https://doi.org/10.1016/j.fitote.2007.02.007

Bulbul, I. J., Shanta, A. P., & Rashid, M. A. (2022). Evaluation of antidiarrheal activity of *Leea aequata* L. (family: Vitaceae) in mice models. *Bangladesh Pharmaceutical Journal*, *25*(2), 180–187. https://doi.org/10.3329/bpj.v25i2.60969

Checker, R., Sandur, S. K., Sharma, D., Patwardhan, R. S., Jayakumar, S., Kohli, V., Sethi, G., Aggarwal, B. B., & Sainis, K. B. (2012). The potent anti-inflammatory activity of ursolic acid, a triterpenoid antioxidant, is mediated through suppression of NF-κB, AP-1 and NF-AT. *PLoS ONE*, *7*(2). https://doi.org/10.1371/journal.pone.0031318

Choudhary M.S and Upadhyaym U. (2012). A study on indigenous herbal remedies used to cure jaundice by tribal's from Central Narmada of Madhya Pradesh. *Life sciences Leaflets*, 1, 1–5.

Cikman, O., Soylemez, O., Ozkan, O. F., Kiraz, H. A., Sayar, I., Ademoglu, S., Taysi, S., & Karaayvaz, M. (2015). Antioxidant activity of syringic acid prevents oxidative stress in l-arginine-induced acute pancreatitis: An experimental study on rats. *International Surgery*, *100*(5), 891–896. https://doi.org/10.9738/INTSURG-D-14-00170.1

Cui, F., Li, M. X., Chang, H. J., Mao, Y., Zhang, H. Y., Lu, L. X., Yan, S. G., Lang, M. L., Liu, L., & Qiao, C. L. (2015). Carboxylesterase-mediated insecticide resistance: Quantitative increase induces broader metabolic resistance than qualitative change. *Pesticide Biochemistry and Physiology*, *121*, 88–96. https://doi.org/10.1016/j.pestbp.2014.12.016

Dalu, D., Duggirala, S., & Akarapu, S. (2014). Anti hyperglycemic and hypolipidemic activity of. *International Jornal of Bioassays*, *3*(7), 3155–3159. https://doi.org/10.13140/RG.2.2.14200.14086

Das, N., Hossain, S., Barmon, J., Parvin, S., Hasan, M., Akter, M., & Islam, E. (2021). Evaluation of *Leea rubra* leaf extract for oxidative damage protection and antitumor and antimicrobial potential. *Journal of Tropical Medicine*, *2021*. https://doi.org/10.1155/2021/7239291

Das, N., Parvin, M. S., Hasan, M., Akter, M., Hossain, M. S., Parvez, G. M. M., Sarker, A. K., Abdur Rahman, M. A., Mamun, A., & Islam, M. E. (2022). A flavone from the ethyl acetate extract of Leea rubra leaves with DNA damage protection and antineoplastic activity. *Biochemistry and Biophysics Reports*, *30*(January), 101244. https://doi.org/10.1016/j.bbrep.2022.101244

Das, S., Singh, V. K., Chaudhari, A. K., Deepika, Dwivedy, A. K., & Dubey, N. K. (2022). Co-encapsulation of *Pimpinella anisum* and *Coriandrum sativum* essential oils based synergistic formulation through binary mixture: Physico-chemical characterization, appraisal of antifungal mechanism of action, and application as natural food preservative. *Pesticide Biochemistry and Physiology*, 105066. https://doi.org/10.1016/j.pestbp.2022.105066

De Beck, P. O., Cartier, G., David, B., Dijoux-Franca, M. G., & Mariotte, A. M. (2003). Antioxidant flavonoids and phenolic acids from leaves of *Leea guineense* G. Don (Leeaceae). *Phytotherapy Research*, *17*(4), 345–347. https://doi.org/10.1002/ptr.1141

Do Nascimento, P. G. G., Lemos, T. L. G., Bizerra, A. M. C., Arriaga, A. M. C., Ferreira, D. A., Santiago, G. M. P., Braz-Filho, R., & Costa, J. G. M. (2014). Antibacterial and antioxidant activities of ursolic acid and derivatives. *Molecules*, *19*(1), 1317–1327. https://doi.org/10.3390/molecules19011317

Domitrović, R., Rashed, K., Cvijanović, O., Vladimir-Knežević, S., Škoda, M., & Višnić, A. (2015). Myricitrin exhibits antioxidant, anti-inflammatory and antifibrotic activity in carbon tetrachloride-intoxicated mice. *Chemico-Biological Interactions*, *230*, 21–29. https://doi.org/10.1016/j.cbi.2015.01.030

Dong, Z. W., & Yuan, Y. F. (2018). Juglanin

suppresses fibrosis and inflammation response caused by LPS in acute lung injury. *International Journal of Molecular Medicine*, *41*(6), 3353–3365. https://doi.org/10.3892/ijmm.2018.3554

Ebada, S. S., Al-Jawabri, N. A., Youssef, F. S., El-Kashef, D. H., Knedel, T. O., Albohy, A., Korinek, M., Hwang, T. L., Chen, B. H., Lin, G. H., Lin, C. Y., Aldalaien, S. M., Disi, A. M., Janiak, C., & Proksch, P. (2020). Anti-inflammatory, antiallergic and COVID-19 protease inhibitory activities of phytochemicals from the Jordanian hawksbeard: Identification, structure-Activity relationships, molecular modeling and impact on its folk medicinal uses. *RSC Advances*, *10*(62), 38128–38141. https://doi.org/10.1039/d0ra04876c

Ekaprasada, M. T., Nurdin, H., Ibrahim, S., & Dachriyanus, D. (2010). Antioxidant activity of methyl gallate isolated from the leaves of *Toona sureni*. *Indonesian Journal of Chemistry*, *9*(3), 457–460. https://doi.org/10.22146/ijc.21515

El-Hawary, S. S., Mohammed, R., Abouzid, S., Ali, Z. Y., & Elwekeel, A. (2016). Anti-arthritic activity of 11-O-(4′-O-methyl galloyl)-bergenin and *Crassula capitella* extract in rats. *Journal of Pharmacy and Pharmacology*, *68*(6), 834–844. https://doi.org/10.1111/jphp.12566

El-Saber Batiha, G., Beshbishy, A. M., Ikram, M., Mulla, Z. S., Abd El-Hack, M. E., Taha, A. E., Algammal, A. M., & Ali Elewa, Y. H. (2020). The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: Quercetin. *Foods*, *9*(3). https://doi.org/10.3390/foods9030374

Elloumi, W., Mahmoudi, A., Ortiz, S., Boutefnouchet, S., Chamkha, M., & Sayadi, S. (2022). Wound healing potential of quercetin-3-O-rhamnoside and myricetin-3-O-rhamnoside isolated from Pistacia lentiscus distilled leaves in rats model. *Biomedicine and Pharmacotherapy*, *146*, 112574. https://doi.org/10.1016/j.biopha.2021.112574

Falodun, A., Okunrobo, L. O., & Agbo, L. O. (2007). Evaluation of the anti-edematogenic activity of the aqueous extract of Leea guineensis. *Pakistan Journal of Scientific and Industrial Research*, *50*(2), 143–144.

Ferdousy, S., Rahman, M. A., Al-Amin, M. M., Aklima, J., & Chowdhury, J. M. K. H. (2017). Antioxidative and neuroprotective effects of Leea macrophylla methanol root extracts on diazepam-induced memory impairment in amnesic Wistar albino rat. *Clinical Phytoscience*, *2*(1). https://doi.org/10.1186/s40816-016-0031-6

Fuentes-Rios, D., Cepero, A., García-Castro, M., Contreras-Cáceres, R., López-Romero, J. M., Luque, C., Cabeza, L., Melguizo, C., & Prados, J. (2022). Synthesis, solubility and antitumor activity of maslinic acid derivatives. *European Journal of Medicinal Chemistry Reports*, *4*(October 2021), 100032. https://doi.org/10.1016/j.ejmcr.2022.100032

Ghagane, S. C., Puranik, S. I., Kumbar, V. M., Nerli, R. B., Jalalpure, S. S., Hiremath, M. B., Neelagund, S., & Aladakatti, R. (2017). In vitro antioxidant and anticancer activity of *Leea indica* leaf extracts on human prostate cancer cell lines. *Integrative Medicine Research*, *6*(1), 79–87. https://doi.org/10.1016/j.imr.2017.01.004

Ginting, N., Suwarso, E., Rumapea, D. V., & Nerdy, N. (2018). Relaxation activity of tetanus (*Leea aequata* L.) leaf ethanolic extract on guinea pig isolated trachea. *Asian Journal of Pharmaceutical and Clinical Research*, *11*(April), 24–27. https://doi.org/10.22159/ajpcr.2018.v11s1.26557

Gonzales, D. C. M., Bilale, V. H., Dinglasan, B. A., Garcia, H. R. E., Hasan, Z. S. A., & Magtibay, C. R. M. (2019). In vitro xanthine oxidase inhibition of ethanolic crude leaf extract from *Leea aculeata* (Mali-mali). The Steth, *13*, 16–33.

Gopal, J., Muthu, M., Paul, D., Kim, D. H., & Chun, S. (2016). Bactericidal activity of green tea extracts: The importance of catechin containing nano particles. *Scientific Reports*, *6*, 1–14. https://doi.org/10.1038/srep19710

Guo, R., Liu, Y., Pan, J., Guan, W., Yang, B. Y., & Kuang, H. X. (2021). A new sesquiterpenoid with cytotoxic and anti-inflammatory activity from the leaves of *Datura metel* L. *Natural Product Research*, *35*(4), 607–613. https://doi.org/10.1080/14786419.2019.1590715

Gutiérrez-Rebolledo, G. A., Siordia-Reyes, A. G., Meckes-Fischer, M., & Jiménez-Arellanes, A. (2016). Hepatoprotective properties of oleanolic and ursolic acids in antitubercular drug-induced liver damage. *Asian Pacific*

Journal of Tropical Medicine, *9*(7), 644–651. https://doi.org/10.1016/j.apjtm.2016.05.015

Hidayah, T., & Barlian, A. (2022). Peran ekstrak kulit batang *Leea angulata* pada tahap proliferasi dalam proses penyembuhan luka kulit mencit (*Mus musculus*) (The role of *Leea angulata* stem bark extract at the proliferation stage in the skin wound healing process of mice (*Mus musculus*)). *Jurnal Sumberdaya Hayati*, *7*(2), 71–77. https://doi.org/10.29244/jsdh.7.2.71-77

Hong, E. Y., Kim, T. Y., Hong, G. U., Kang, H., Lee, J. Y., Park, J. Y., Kim, S. C., Kim, Y. H., Chung, M. H., Kwon, Y. I., & Ro, J. Y. (2019). Inhibitory effects of roseoside and icariside E4 isolated from a natural product mixture (NO-AP) on the expression of angiotensin II receptor 1 and oxidative stress in angiotensin II-stimulated H9c2 cells. *Molecules*, *24*(3), 1–13. https://doi.org/10.3390/molecules24030414

Hossain, F., Mostofa, M. G., & Alam, A. K. (2021). Traditional uses and pharmacological activities of the genus leea and its phytochemicals: A review. *Heliyon*, *7*(2), e06222–e06222. https://doi.org/10.1016/j.heliyon.2021.e06222

Hossain, K. H., Rahman, M. A., Taher, M., Tangpong, J., Hajjar, D., Alelwani, W., Makki, A. A., & Ali Reza, A. S. M. (2020). Hot methanol extract of *Leea macrophylla* (Roxb.) manages chemical-induced inflammation in rodent model. *Journal of King Saud University - Science*, *32*(6), 2892–2899. https://doi.org/10.1016/j.jksus.2020.07.014

Hwang, B., Cho, J., Hwang, I. sok, Jin, H. G., Woo, E. R., & Lee, D. G. (2011). Antifungal activity of lariciresinol derived from *Sambucus williamsii* and their membrane-active mechanisms in *Candida albicans*. *Biochemical and Biophysical Research Communications*, *410*(3), 489–493. https://doi.org/10.1016/j.bbrc.2011.06.004

Islam, M. B., Sarkar, M. M. H., Shafique, M. Z., Jalil, M. A., Haque, M. Z., & Amin, R. (2013). Phytochemical screening and anti-microbial activity studies on *Leea macrophylla* seed extracts. *Journal of Scientific Research*, *5*(2), 399–405. https://doi.org/10.3329/jsr.v5i2.13213

Jesus, J. A., Lago, J. H. G., Laurenti, M. D., Yamamoto, E. S., & Passero, L. F. D. (2015). Antimicrobial activity of oleanolic and ursolic acids: An update. *Evidence-Based Complementary and Alternative Medicine*, *2015*(Figure 1). https://doi.org/10.1155/2015/620472

Joshi, A., Joshi, V. K., Pandey, D., & Hemalatha, S. (2016). Systematic investigation of ethanolic extract from Leea macrophylla: Implications in wound healing. *Journal of Ethnopharmacology*, *191*, 95–106. https://doi.org/10.1016/j.jep.2016.06.034

Kadchumsang, S., Sirisa-Ard, P., Sookkhee, S., Eakanunkul, S., & Chansakaow, S. (2014). Antibacterial and antioxidant activities of various fraction of *Leea rubra* (Leeaceae). *Journal of Natural Sciences Research Www*, *4*(11), 2225–2921.

Kaewkrud, W., Otsuka, H., Ruchirawat, S., & Kanchanapoom, T. (2007). Leeaoside, a new megastigmane diglycoside from the leaves of *Leea thorelii* Gagnep. *Journal of Natural Medicines*, *61*(4), 449–451. https://doi.org/10.1007/s11418-007-0170-7

Kahkeshani, N., Farzaei, F., Fotouhi, M., Alavi, S. S., Bahramsoltani, R., Naseri, R., Momtaz, S., Abbasabadi, Z., Rahimi, R., Farzaei, M. H., & Bishayee, A. (2019). Pharmacological effects of gallic acid in health and disease: A mechanistic review. *Iranian Journal of Basic Medical Sciences*, *22*(3), 225–237. https://doi.org/10.22038/ijbms.2019.32806.7897

Khan, H., Amin, H., Ullah, A., Saba, S., Rafique, J., Khan, K., Ahmad, N., & Badshah, S. L. (2016). Antioxidant and antiplasmodial activities of bergenin and 11-O-galloylbergenin isolated from *Mallotus philippensis*. *Oxidative Medicine and Cellular Longevity*, *2016*. https://doi.org/10.1155/2016/1051925

Khan, M. R., Omoloso, A. D., & Kihara, M. (2003). Antibacterial activity of alstonia scholaris and *Leea tetramera*. *Fitoterapia*, *74*(7–8), 736–740. https://doi.org/10.1016/S0367-326X(03)00192-8

Khwaza, V., Oyedeji, O. O., & Aderibigbe, B. A. (2020). Ursolic acid-based derivatives as potential anti-cancer agents: An update. *International Journal of Molecular Sciences*, *21*(16), 1–27. https://doi.org/10.3390/ijms21165920

Kicel, A., & Wolbiś, M. (2012). Study on the phenolic constituents of the flowers and leaves of *Trifolium repens* L. *Natural Product Research*, *26*(21), 2050–2054.

https://doi.org/10.1080/14786419.2011.637217

Kil, H. W., Rho, T., & Yoon, K. D. (2019). Phytochemical study of aerial parts of *Leea asiatica*. *Molecules*, *24*(9), 1–11. https://doi.org/10.3390/molecules24091733

Kim, S. J., Cha, J. Y., Kang, H. S., Lee, J. H., Lee, J. Y., Park, J. H., Bae, J. H., Song, D. K., & Im, S. S. (2016). Corosolic acid ameliorates acute inflammation through inhibition of IRAK-1 phosphorylation in macrophages. *BMB Reports*, *49*(5), 276–281. https://doi.org/10.5483/BMBRep.2016.49.5.241

Koriem, K.M.M., Aminuddin, M.E., Kader, A.S., & Sheikh, N.R. (2013). Antihyperglycemic, antihyperlipidemic and antiapoptotic activities of *Micromelum minutum* seeds in diabetic rats. *Journal of Molecular and Genetic Medicine*, *s1*(01). https://doi.org/10.4172/1747-0862.s1-004

Kong, C. S., & Seo, Y. (2012). Antiadipogenic activity of isohamnetin 3-O-β-D-glucopyranoside from *Salicornia herbacea*. *Immunopharmacology and Immunotoxicology*, *34*(6), 907–911. https://doi.org/10.3109/08923973.2012.670643

Kujur, M. (2010). Antibacterial activity of seeds stems and roots of *Leea aequata*. *Biosciences, Biotechnology Research Asia, 7*(1), 453–456.

Lakornwong, W., Kanokmedhakul, K., & Kanokmedhakul, S. (2014). Chemical constituents from the roots of *Leea thorelii* Gagnep. *Natural Product Research*, *28*(13), 1015–1017. https://doi.org/10.1080/14786419.2014.891117

Lee, W., Yang, E. J., Ku, S. K., Song, K. S., & Bae, J. S. (2013). Anti-inflammatory effects of oleanolic acid on LPS-induced inflammation in vitro and in vivo. *Inflammation*, *36*(1), 94–102. https://doi.org/10.1007/s10753-012-9523-9

Lemos, A. S. O., Florêncio, J. R., Pinto, N. C. C., Campos, L. M., Silva, T. P., Grazul, R. M., Pinto, P. F., Tavares, G. D., Scio, E., Apolônio, A. C. M., Melo, R. C. N., & Fabri, R. L. (2020). Antifungal activity of the natural coumarin scopoletin against planktonic cells and biofilms from a multidrug-resistant *Candida tropicalis* strain. *Frontiers in Microbiology*, *11*(July), 1–11. https://doi.org/10.3389/fmicb.2020.01525

Li, T., Pan, H., Feng, Y., Li, H., & Zhao, Y. (2015). Bioactivity-guided isolation of anticancer constituents from *Hedera nepalensis* K. Koch. *South African Journal of Botany*, *100*(30), 87–93. https://doi.org/10.1016/j.sajb.2015.05.011

Liese, J., Abhari, B. A., & Fulda, S. (2015). Smac mimetic and oleanolic acid synergize to induce cell death in human hepatocellular carcinoma cells. *Cancer Letters*, *365*(1), 47–56. https://doi.org/10.1016/j.canlet.2015.04.018

Ma, B., Zhang, H., Wang, Y., Zhao, A., Zhu, Z., Bao, X., Sun, Y., Li, L., & Zhang, Q. (2018). Corosolic acid, a natural triterpenoid, induces ER stress-dependent apoptosis in human castration resistant prostate cancer cells via activation of IRE-1/JNK, PERK/CHOP and TRIB3. *Journal of Experimental and Clinical Cancer Research*, *37*(1), 1–16. https://doi.org/10.1186/s13046-018-0889-x

Mahmud, Z. Al, Bachar, S. C., Hasan, C. M., Emran, T. Bin, Qais, N., & Uddin, M. M. N. (2017). Phytochemical investigations and antioxidant potential of roots of Leea macrophylla (Roxb.). *BMC Research Notes*, *10*(1), 1–9. https://doi.org/10.1186/s13104-017-2503-2

Mawa, J., Rahman, M. A., Hashem, M. A., & Juwel Hosen, M. (2019). *Leea macrophylla* root extract upregulates the mRNA expression for antioxidative enzymes and repairs the necrosis of pancreatic β-cell and kidney tissues in fructose-fed type 2 diabetic rats. *Biomedicine and Pharmacotherapy*, *110*(October 2018), 74–84. https://doi.org/10.1016/j.biopha.2018.11.033

Min, K., & Kwon, T. K. (2014). Anticancer effects and molecular mechanisms of epigallocatechin-3-gallate. *Integrative Medicine Research*, *3*(1), 16–24. https://doi.org/10.1016/j.imr.2013.12.001

Mokhtari, K., Rufino-Palomares, E. E., Pérez-Jiménez, A., Reyes-Zurita, F. J., Figuera, C., García-Salguero, L., Medina, P. P., Peragón, J., & Lupiáñez, J. A. (2015). Maslinic acid, a triterpene from olive, affects the antioxidant and mitochondrial status of B16F10 melanoma cells grown under stressful conditions. *Evidence-Based Complementary and Alternative Medicine*, *2015*.

https://doi.org/10.1155/2015/272457

Motlhatlego, K. E., Abdalla, M. A., Leonard, C. M., Eloff, J. N., & McGaw, L. J. (2020). Inhibitory effect of newtonia extracts and myricetin-3-o-rhamnoside (myricitrin) on bacterial biofilm formation. *BMC Complementary Medicine and Therapies*, *20*(1), 1–10. https://doi.org/10.1186/s12906-020-03139-4

Nishioka, T., Watanabe, J., Kawabata, J., & Niki, R. (1997). Isolation and activity of N-p-coumaroyltyramine, an α-glucosidase inhibitor in welsh onion (allium fistulosum). *Bioscience, Biotechnology and Biochemistry*, *61*(7), 1138–1141. https://doi.org/10.1271/bbb.61.1138

Nizami, A. N., Rahman, M. A., Ahmed, N. U., & Islam, M. S. (2012). Whole *Leea macrophylla* ethanolic extract normalizes kidney deposits and recovers renal impairments in an ethylene glycol-induced urolithiasis model of rats. *Asian Pacific Journal of Tropical Medicine*, *5*(7), 533–538. https://doi.org/10.1016/S1995-7645(12)60094-7

Nyunt, K. S., Elkhateeb, A., Tosa, Y., Nabata, K., Katakura, K., & Matsuura, H. (2012). Isolation of antitrypanosomal compounds from *Vitis repens,* a medicinal plant of Myanmar. *Natural Product Communications*, *7*(5), 609–610. https://doi.org/10.1177/1934578x1200700516

Pratiwi, R., Nantasenamat, C., Ruankham, W., Suwanjang, W., Prachayasittikul, V., Prachayasittikul, S., & Phopin, K. (2021). Mechanisms and neuroprotective activities of stigmasterol against oxidative stress-induced neuronal cell death via sirtuin family. *Frontiers in Nutrition*, *8*(May), 1–12. https://doi.org/10.3389/fnut.2021.648995

Qian, W., Fu, Y., Liu, M., Wang, T., Zhang, J., Yang, M., Sun, Z., Li, X., & Li, Y. (2020). In vitro antibacterial activity and mechanism of vanillic acid against carbapenem-resistant *Enterobacter cloacae*. *Antibiotics*, *9*(June), 322.

Qian, W., Wang, W., Zhang, J., Wang, T., Liu, M., Yang, M., Sun, Z., Li, X., & Li, Y. (2020). Antimicrobial and antibiofilm activities of ursolic acid against carbapenem-resistant *Klebsiella pneumoniae*. *Journal of Antibiotics*, *73*(6), 382–391. https://doi.org/10.1038/s41429-020-0285-6

Rahim, A., Mostofa, M. G., Sadik, M. G., Rahman, M. A. A., Khalil, M. I., Tsukahara, T., Nakagawa-Goto, K. K., & Alam, A. K. (2021). The anticancer activity of two glycosides from the leaves of *Leea aequata* L. *Natural Product Research*, *35*(24), 5867–5871. https://doi.org/10.1080/14786419.2020.1798661

Rahman, M. A., Imran, T. bin, & Islam, S. (2013). Antioxidative, antimicrobial and cytotoxic effects of the phenolics of *Leea indica* leaf extract. *Saudi Journal of Biological Sciences*, *20*(3), 213–225. https://doi.org/10.1016/j.sjbs.2012.11.007

Rahman, M. A., Sultana, R., Bin Emran, T., Islam, M. S., Rahman, M. A., Chakma, J. S., Rashid, H. ur, & Hasan, C. M. M. (2013). Effects of organic extracts of six Bangladeshi plants on in vitro thrombolysis and cytotoxicity. *BMC Complementary and Alternative Medicine*, *13*. https://doi.org/10.1186/1472-6882-13-25

Raihan, M. O., Habib, M. R., Brishti, A., Rahman, M. M., Saleheen, M. M., & Manna, M. (2011). Sedative and anxiolytic effects of the methanolic extract of *Leea indica* (Burm. f.) Merr. leaf. *Drug Discoveries & Therapeutics*, *5*(4), 185–189. https://doi.org/10.5582/ddt.2011.v5.4.185

Reddy, N. S., Navanesan, S., Sinniah, S. K., Wahab, N. A., & Sim, K. S. (2012). Phenolic content, antioxidant effect and cytotoxic activity of *Leea indica* leaves. *BMC Complementary and Alternative Medicine*, *12*, 1–7. https://doi.org/10.1186/1472-6882-12-128

Riaz, A., Rasul, A., Hussain, G., Zahoor, M. K., Jabeen, F., Subhani, Z., Younis, T., Ali, M., Sarfraz, I., & Selamoglu, Z. (2018). Astragalin: A bioactive phytochemical with potential therapeutic activities. *Advances in Pharmacological Sciences*, *2018*. https://doi.org/10.1155/2018/9794625

SaeYoon, A., Sukkarn, B., Nosoongnoen, W., Jantarat, C., Hiransai, P., Sakdiset, P., Chingunpitak, J., Makchuchit, S., & Itharat, A. (2015). Withdrawn: Determination of N-trans-feruloyltyramine content and nitric oxide inhibitory and antioxidant activities of *Tinospora crispa*. *Asian Journal of Pharmaceutical Sciences*, 10–11. https://doi.org/10.1016/j.ajps.2015.11.001

Santiago, L., & Bartolome, M. (2015). Chromatographic separation of the free radical scavenging components of the leaf extracts of *Leea philippinensis* Merr. *International Food Research Journal*, *22*(4),

1396–1403. http://agris.upm.edu.my:8080/dspace/handle/0/12610

Sen, S., De, B., Devanna, N., & Chakraborty, R. (2013). Cisplatin-induced nephrotoxicity in mice: Protective role of *Leea asiatica* leaves. *Renal Failure*, *35*(10), 1412–1417. https://doi.org/10.3109/0886022X.2013.829405

Sen, S., De, B., Devanna, N., & Chakraborty, R. (2014). Hepatoprotective and antioxidant activity of *Leea asiatica* leaves against acetaminophen-induced hepatotoxicity in rats. *Tang [Humanitas Medicine]*, *4*(3), 18.1-18.5. https://doi.org/10.5667/tang.2014.0005

Siew, Y. Y., Yew, H. C., Neo, S. Y., Seow, S. V., Lew, S. M., Lim, S. W., Lim, C. S. E. S., Ng, Y. C., Seetoh, W. G., Ali, A., Tan, C. H., & Koh, H. L. (2019). Evaluation of anti-proliferative activity of medicinal plants used in Asian traditional medicine to treat cancer. *Journal of Ethnopharmacology*, *235*(December 2018), 75–87. https://doi.org/10.1016/j.jep.2018.12.040

Sifaoui, I., López-Arencibia, A., Martín-Navarro, C. M., Reyes-Batlle, M., Mejri, M., Valladares, B., Lorenzo-Morales, J., Abderabba, M., & Piñero, J. E. (2017). Selective activity of oleanolic and maslinic acids on the amastigote form of *Leishmania spp. Iranian Journal of Pharmaceutical Research*, *16*(3), 1192–1195.

Singh, D., Siew, Y. Y., Chong, T. I., Yew, H. C., Ho, S. S. W., Lim, C. S. E. S., Tan, W. X., Neo, S. Y., & Koh, H. L. (2019). Identification of phytoconstituents in *Leea indica* (Burm. F.) Merr. leaves by high performance liquid chromatography micro time-of-flight mass spectrometry. *Molecules*, *24*(4), 5–12. https://doi.org/10.3390/molecules24040714

Singh, H., Lily, M. K., & Dangwal, K. (2015). Evaluation and comparison of polyphenols and bioactivities of wild edible fruits of North-West Himalaya, India. *Asian Pacific Journal of Tropical Disease*, *5*(11), 888–893. https://doi.org/10.1016/S2222-1808(15)60951-3

Sung, H. Y., Kang, S. W., Kim, J. L., Li, J., Lee, E. S., Gong, J. H., Han, S. J., & Kang, Y. H. (2010). Oleanolic acid reduces markers of differentiation in 3T3-L1 adipocytes. *Nutrition Research*, *30*(12), 831–839. https://doi.org/10.1016/j.nutres.2010.10.001

Suresh N. Nair, Meera S. Nair, Divek V. T. Nair, S. Juliet, S. K. Padinchareveetil, S. Samraj, R. R. (2014). Wound healing, anti inflamatory activity and toxicological studies of *Leea asiatica* (L.) Rishdale. *International Journal of Biological and Pharmaceutical Research*, *September*.

Tun, N. L., Hu, D. B., Xia, M. Y., Zhang, D. D., Yang, J., Oo, T. N., Wang, Y. H., & Yang, X. F. (2019). Chemical constituents from ethanoic extracts of the aerial parts of *Leea aequata* L., a traditional folk medicine of Myanmar. *Natural Products and Bioprospecting*, *9*(3), 243–249. https://doi.org/10.1007/s13659-019-0209-y

Utari, F., Itam, A., Syafrizayanti, S., Putri, W. H., Ninomiya, M., Koketsu, M., Tanaka, K., & Efdi, M. (2019). Isolation of flavonol rhamnosides from *Pometia pinnata* leaves and investigation of α-glucosidase inhibitory activity of flavonol derivatives. *Journal of Applied Pharmaceutical Science*, *9*(8), 53–65. https://doi.org/10.7324/JAPS.2019.90808

Uy M, M., & G.L Villazorda, M. (2015). The antioxidant properties of the Philippine medicinal plants *Cassia sophera* Linn., *Derris elliptica* Benth, *Ficus minahassea* Tesym. and De Vr., *Leea aculeata* Blume and *Leucosyke capitellata* Wedd. *AAB BIOFLUX Advances in Agriculture & Botanics- International Journal of the Bioflux Society*, *7*(3), 150–156. http://www.aab.bioflux.com.ro

Valentová, K., Vrba, J., Bancířová, M., Ulrichová, J., & Křen, V. (2014). Isoquercitrin: Pharmacology, toxicology, and metabolism. *Food and Chemical Toxicology*, *68*, 267–282. https://doi.org/10.1016/j.fct.2014.03.018

Walker, J., Reichelt, K. V., Obst, K., Widder, S., Hans, J., Krammer, G. E., Ley, J. P., & Somoza, V. (2016). Identification of an anti-inflammatory potential of: Eriodictyon angustifolium compounds in human gingival fibroblasts. *Food and Function*, *7*(7), 3046–3055. https://doi.org/10.1039/c6fo00482b

Wang, J., Huang, M., Yang, J., Ma, X., Zheng, S., Deng, S., Huang, Y., Yang, X., & Zhao, P. (2017). Anti-diabetic activity of stigmasterol from soybean oil by targeting the GLUT4 glucose transporter. *Food and Nutrition Research*, *61*(1). https://doi.org/10.1080/16546628.2017.1364117

Wang, J., Ren, H., Xu, Q. L., Zhou, Z. Y., Wu, P., Wei, X.

Y., Cao, Y., Chen, X. X., & Tan, J. W. (2015). Antibacterial oleanane-type triterpenoids from pericarps of *Akebia trifoliata*. *Food Chemistry*, *168*, 623–629. https://doi.org/10.1016/j.foodchem.2014.07.105

Wong, K. C., Cao, S., Dong, X., Law, M. C., Chan, T. H., & Wong, M. S. (2017). (—)-Epiafzelechin protects against ovariectomy-induced bone loss in adult mice and modulate osteoblastic and osteoclastic functions in vitro. *Nutrients*, *9*(5), 1–14. https://doi.org/10.3390/nu9050530

Wong, Y. H., & Abdul Kadir, H. (2012). Induction of mitochondria-mediated apoptosis in ca ski human cervical cancer cells triggered by mollic acid arabinoside isolated from *Leea indica*. *Evidence-Based Complementary and Alternative Medicine*, *2012*. https://doi.org/10.1155/2012/684740

Wong, Y. H., Abdul Kadir, H., & Ling, S. K. (2012). Bioassay-guided isolation of cytotoxic cycloartane triterpenoid glycosides from the traditionally used medicinal plant *Leea indica. Evidence-Based Complementary and Alternative Medicine*, *2012*. https://doi.org/10.1155/2012/164689

Woode, E., Alagpulinsa, D. A., & Abotsi, W. K. M. (2011). Anti-nociceptive, anxiolytic and anticonvulsant effects of an aqueous leaf extract of *Leea guineensis* G. Don (Family: Leeaceae). *African Journal of Pharmacy and Pharmacology*, *5*(8), 1132–1144. https://doi.org/10.5897/AJPP10.407

Xu, S., Wang, G., Peng, W., Xu, Y., Zhang, Y., Ge, Y., Jing, Y., & Gong, Z. (2019). Corosolic acid isolated from *Eriobotrya japonica* leaves reduces glucose level in human hepatocellular carcinoma cells, zebrafish and rats. *Scientific Reports*, *9*(1), 1–13. https://doi.org/10.1038/s41598-019-40934-7

Yang, M. H., Ali, Z., Khan, I. A., & Khan, S. I. (2014). Anti-inflammatory activity of constituents isolated from *Terminalia chebula*. *Natural Product Communications*, *9*(7), 965–968. https://doi.org/10.1177/1934578x1400900721

Zhao, L., Chen, J., Su, J., Li, L., Hu, S., Li, B., Zhang, X., Xu, Z., & Chen, T. (2013). In vitro antioxidant and antiproliferative activities of 5-hydroxymethylfurfural. *Journal of Agricultural and Food Chemistry*, *61*(44), 10604–10611. https://doi.org/10.1021/jf403098y

Zhu, K. C., Sun, J. M., Shen, J. G., Jin, J. Z., Liu, F., Xu, X. L., Chen, L., Liu, L. T., & Lv, J. J. (2015). Afzelin exhibits anti-cancer activity against androgen-sensitive LNCaP and androgen-independent PC-3 prostate cancer cells through the inhibition of LIM domain kinase 1. *Oncology Letters*, *10*(4), 2359–2365. https://doi.org/10.3892/ol.2015.3619