



Review article

Traditional uses and pharmacological activities of the genus *Leea* and its phytochemicals: A review

Farhad Hossain, Md. Golam Mostofa, AHM Khurshid Alam*

Department of Pharmacy, University of Rajshahi, Rajshahi, 6205, Bangladesh

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ABSTRACT

Objectives: Plants have been used as traditional medicine (TM) since ancient times and TM remains an effective treatment option in the primary health care system in developing countries, including Bangladesh. There are several reasons to use plants as TM, which are cheaply and easily available and have a cultural heritage of their uses across generations. *Leea*, a genus of the Vitaceae family, possesses a large number of medicinal plants. In this review, the literature data on the traditional uses and pharmacological activities of *Leea* species and their phytochemicals are compiled. All the information was collected from the scientific databases.

Results: *Leea* species are endemic that have opened a promising research field to identify new leads against different diseases. *Leea* contains approximately 70 species, which are widely distributed throughout the Northern and Eastern Australia, South and Southeast Asia and parts of Africa. The *Leea* plants are used traditionally in different ailments such as fever, diarrhea, dysentery, joint pain, rheumatism, diabetes, bone fracture, body ache, wound, sexual disorders, and so on. The majority of the *Leea* species are the medicinal plants, which have anticancer, cytotoxic, antimicrobial, antidiabetic, hepatoprotective, cardiovascular, and CNS activity. Moreover, phytochemicals such as flavonoids, glycosides, phenols, terpenoids, steroids, volatile oils, alkaloids, proteins, quinine derivatives, tannins, saponins, and many other organic compounds have been reported in the *Leea* species (*Leea indica*, *Leea macrophylla*, *Leea asiatica*, *Leea aequata*, *Leea rubra* and *Leea guineensis*). The presence of phytochemicals and the *in vitro* and *in vivo* biological activities reported of these plants support their use as TM. Though original research articles related to the *Leea* genus are available, supportive reviews on phytochemicals and pharmacological activities remain scarce.

Conclusion: *Leea* species are used as TM in different ailments and have a real interest in their diverse pharmacological properties. Also, *Leea* species contain a remarkable number of bioactive compounds. This review has provided a comprehensive report on the plants of *Leea* genus to identify its therapeutic potential and future prospects for betterment research. However, chemical and biological investigations of several species of *Leea* genus remain unexplored. Therefore, further studies on these species are necessary, especially regarding pharmacological properties, isolation of the compounds and mechanism of action for the development of new drugs.

1. Introduction

There is the number of between 750,000 and 1,000,000 plant species in the world. Of these, 500,000 have already been identified and named. About 2000 new flowering plant species are being identified and named each year. Bangladesh is a good repository for plants that have curative and palliative effects on human health, thereby have been used as traditional medicine (TM) in different ailments since ancient times. TM is defined as the sum total of the knowledge, skills, and practices based on the theories, beliefs and experiences indigenous to different cultures,

whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness [1]. TM is very vital and popular in parts of the Asian and African countries. According to World Health Organization (WHO), more than 80% of the populations rely on TM for their primary health care needs in those countries. TM is the oldest form of health care in the world and the outcomes of experimentation through trial and error methods after thousands of years. Historically, different practitioners developed various healing methods to combat a variety of health and life-threatening diseases. TM is also known as complementary and

* Corresponding author.

E-mail address: khurshid.jaist@gmail.com (A.K. Alam).<https://doi.org/10.1016/j.heliyon.2021.e06222>

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alternative or ethnic medicine, and still it plays a key role in many countries today [2, 3]. The knowledge of TM is the support of all other systems of medicine such as Ayurveda, Siddha, Unani, and even modern medicine and it seems to be within everyone's reach and does not require any study or training. Occasionally, TM practitioners are practiced to treat bone fracture, wound healing, poisonous bites, neurological disorders etc. [4, 5]. Accumulating evidence suggests that rural and urban poor people mostly rely on TM and there is no doubt about the efficacy of TM. In fact, this is the only source of health care for such type of population [6].

Plant-based systems continue to play an essential role in healthcare, and their use by different cultures has been extensively documented. According to WHO, the number of plants used for treatment is estimated to be 20,000 named as medicinal plants. The studies on medicinal plants and active substances derived from these have increased the interest in these plants recent years [7]. There are about 45 plant families with 4000 genus that contain these medicinal plants. *Leea* is one of these. *Leea* possesses approximately 70 species that are distributed throughout the Northern and Eastern Australia, New Guinea, South and Southeast Asia and parts of Africa. According to APG IV system, *Leea* is placed in the subfamily of Leeoideae (Vitaceae) [8]. *Leea* is often placed in its own family, Leeaceae, on the basis of morphological differences between Leeaceae and Vitaceae. These differences include the ovule number per locale, carpel number, the absence or presence of a staminoidal tube and floral disc. Pollen structure has also been examined for taxonomic

demarcation and concluded that the pollen structure of Leeaceae and Vitaceae suggests that the families should remain separate while other studies concluded that *Leea* should be included in the Vitaceae family [9].

1.1. Taxonomical classification

Kingdom: Plantae
 Division: Tracheophyta
 Class: Mangoliopsida
 Order: Vitales
 Family: Vitaceae
 Genus: *Leea*

Around 36 out of 70 species of *Leea* are listed on the plant list [10] and are explored as medicinally important herbs in tropical and subtropical countries. According to the Flora of Bangladesh, 7 species such as *Leea asiatica*, *Leea guineensis*, *Leea indica*, *Leea macrophylla*, *Leea aequata*, *Leea rubra* and *Leea alata* of *Leea* are available in Bangladesh [11]. A growing body of evidence suggested that many of these species are traditionally used to treat different ailments such as joint pain, sore, leprosy, eczema, itching, bone fracture, sprain, piles, paralysis, typhoid, rheumatism, cuts injury, sexual weakness, tumor, kidney problems etc. [12, 13]. Many studies reported that the species of *Leea* genus contain a number of bioactive compounds that might possess important pharmacological activities like antimicrobial, antioxidant, anti-diabetic, hepatoprotective, and anticancer activities.

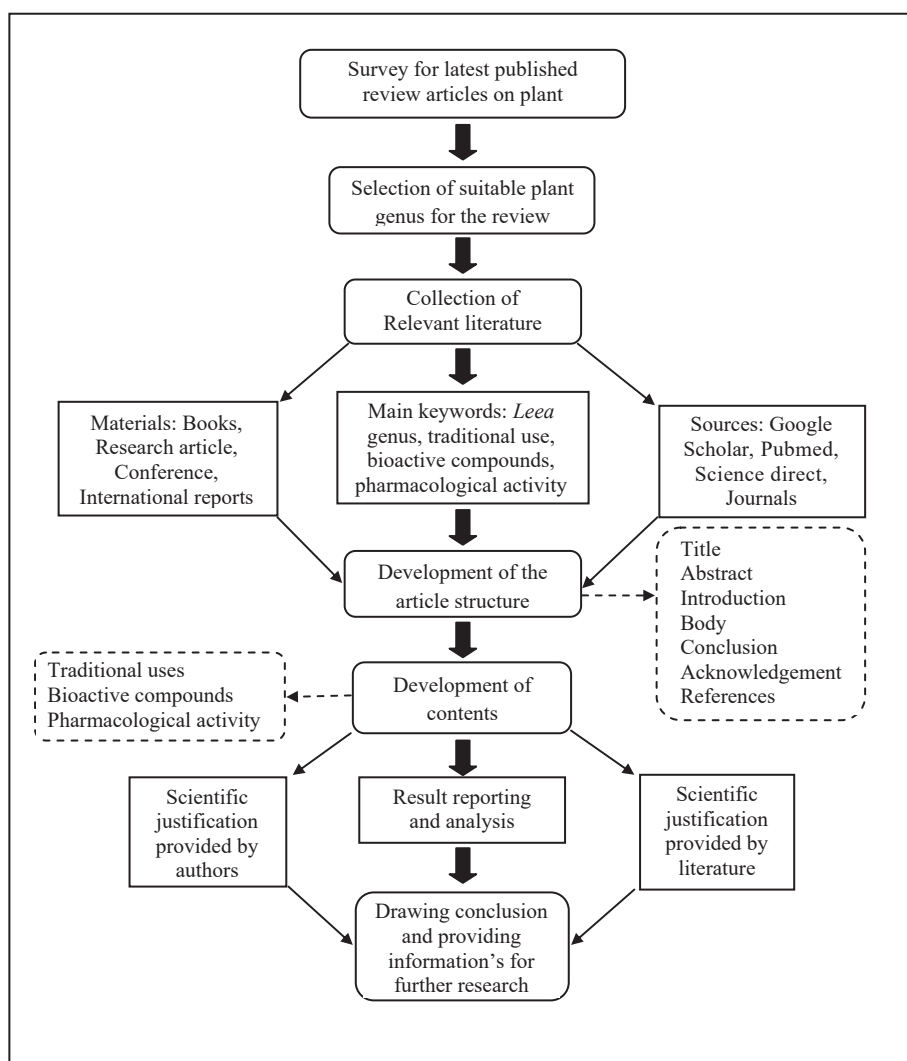


Figure 1. Schematic representation of the methodology of the study.

Review papers generally tend to include both quantitative and narrative or more qualitative components; together, thereby provide platforms for new conceptual frameworks, reveal inconsistencies in the extant body of research, synthesize diverse results, and generally give other scholars a new window for further research. In this review, a comprehensive literature review was carried out to provide an integrated, synthesized overview of the current state of knowledge, develop conceptual frameworks to reconcile and extend past research, describe research insights, existing gaps, and future research directions by providing information regarding traditional uses, bioactive phytochemicals, and pharmacological activities of the species of the genus *Leea*. A literature review was carried out by referring flora, journals and by using

several search engines such as Google scholar, Pubmed, Science direct, Research gate, etc. A schematic diagram (Figure 1) of the methodology of present review study has been incorporated below:

2. Traditional use

The plants of the *Leea* genus have traditional importance worldwide and these plants are predominantly used in the treatment of many life threatening diseases. Many studies reported that various parts (leaf, root, stem, bark, inflorescence and flower) of these plants in certain formulations such as paste and decoction have been used in the treatment of several ailments such as joint pain, sore, leprosy, eczema, itching, bone

Table 1. A list of selected plants belongs to the *Leea* genus, including the plant parts with their traditional uses and the region where these plants are used as TM.

Plant Name	Part	Indications	Region	Reference
<i>Leea indica</i>	Leaf	Joint pain	Chittagong Hill Tracts, Bangladesh	[14]
	Leaf	Joint pain	Jessore District, Bangladesh	[15]
	Leaf and root	Diabetes, cardiac diseases, obstetric diseases, body pain	-	[16]
	Root	Bone fracture	Jalpaiguri district, West Bengal, India	[17]
	Inflorescence, tuber	Chest pain in children (inflorescence extract), allergy (tuber paste)	Rajasthan, India	[18]
	Leaf	Diabetes	Malaysia	[19]
	Leaf and shoot	Wound	Malaysia	[20]
	Root	Diarrhoea, dysentery, hyperdipsia, ulcer, skin diseases	Kerala, India	[21]
	Root, leaf	Diarrhea, dysentery, ulcer	Kerala, India	[22]
	Root	Dysentery	Tamil Nadu, India	[23]
<i>Leea macrophylla</i>	Root	Fracture, rheumatism	Bangladesh	[24]
	Leaf	Tetanus, tonsillitis	Bangladesh	[25]
	Root	Piles	Rajshahi district, Bangladesh	[26]
	Leaf and root	Body pain, paralysis, throbbing pain	Bangladesh	[27]
	Stem and root	Typhoid	Bangladesh	[28]
	Root	Healing cut injury	Bangladesh	[29]
	-	Cancer, dysentery, body-ache, sexual debility	Rajasthan, India	[30]
	-	Tetanus, nephrolithiasis, rheumatism, arthritis, snake bites, sore, pain, blood effusion	Chittagong Hill Tracts, Bangladesh	[31, 32]
	Root	Sexual weakness, tumor	Bangladesh	[33]
	<i>Leea asiatica</i>	-	Worm infection, wound, eye diseases, bone fracture, diabetes, gastrointestinal disorders	India
-		Worm infection, bone fracture, liver disorder, oxidative stress-related diseases	India	[35]
-		Liver disorder	Tripura, India	[36]
Root tuber		Guinea worms, snake-bite	India	[37]
<i>Leea aequata</i>	Bark and root	Astringent, anthelmintic, indigestion, jaundice, chronic fever, malaria.	-	[38]
	Leaf	Wounds, skin diseases	Myanmar	[39]
	Root, stem and tuber	Antiseptic, anesthetics, bronchitis, fever, itching, tuberculosis	Bangladesh	[40]
<i>Leea rubra</i>	-	Gangrene	Bangladesh	[41]
	Root and stem	Intestinal diseases	Thailand	[42]
<i>Leea guineensis</i>	Leaf	Cancer	Guinea	[39]
	-	Pregnancy detection, purgative, toothache, gonorrhoea, general weakness, skin lesions, skin rash, ulcer, diarrhea, paralysis, convulsions, spasm, stomach troubles, herpes and boils	-	[43]
	Leaf	Toothache, rheumatism, skin ulcer, vertigo, epileptic fits, paralysis	West African sub-region	[44]
	Leaf	Enlarged spleen in children	Southern Nigeria	[45]

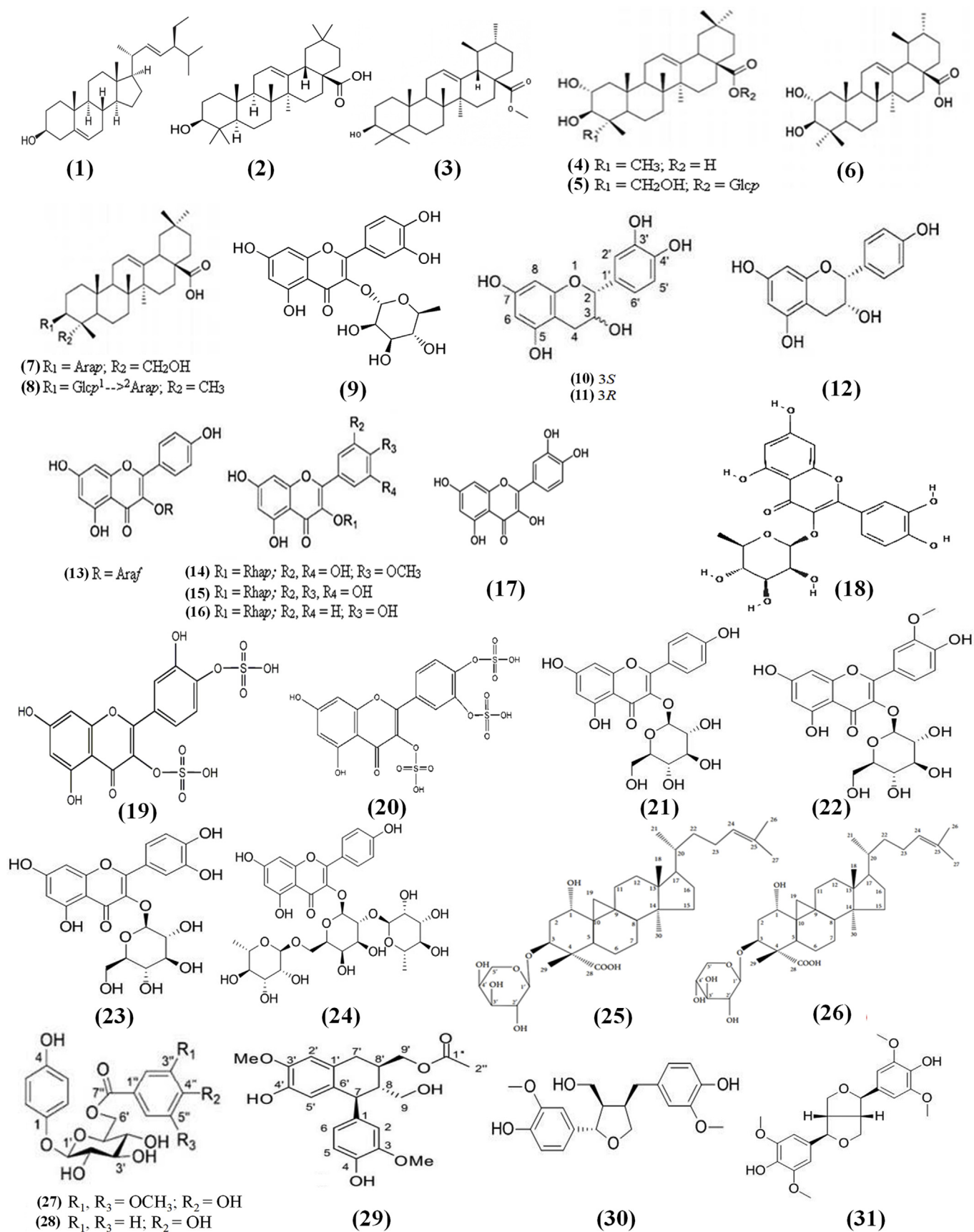


Figure 2. Phytochemicals identified from the species of the genus *Leea*.

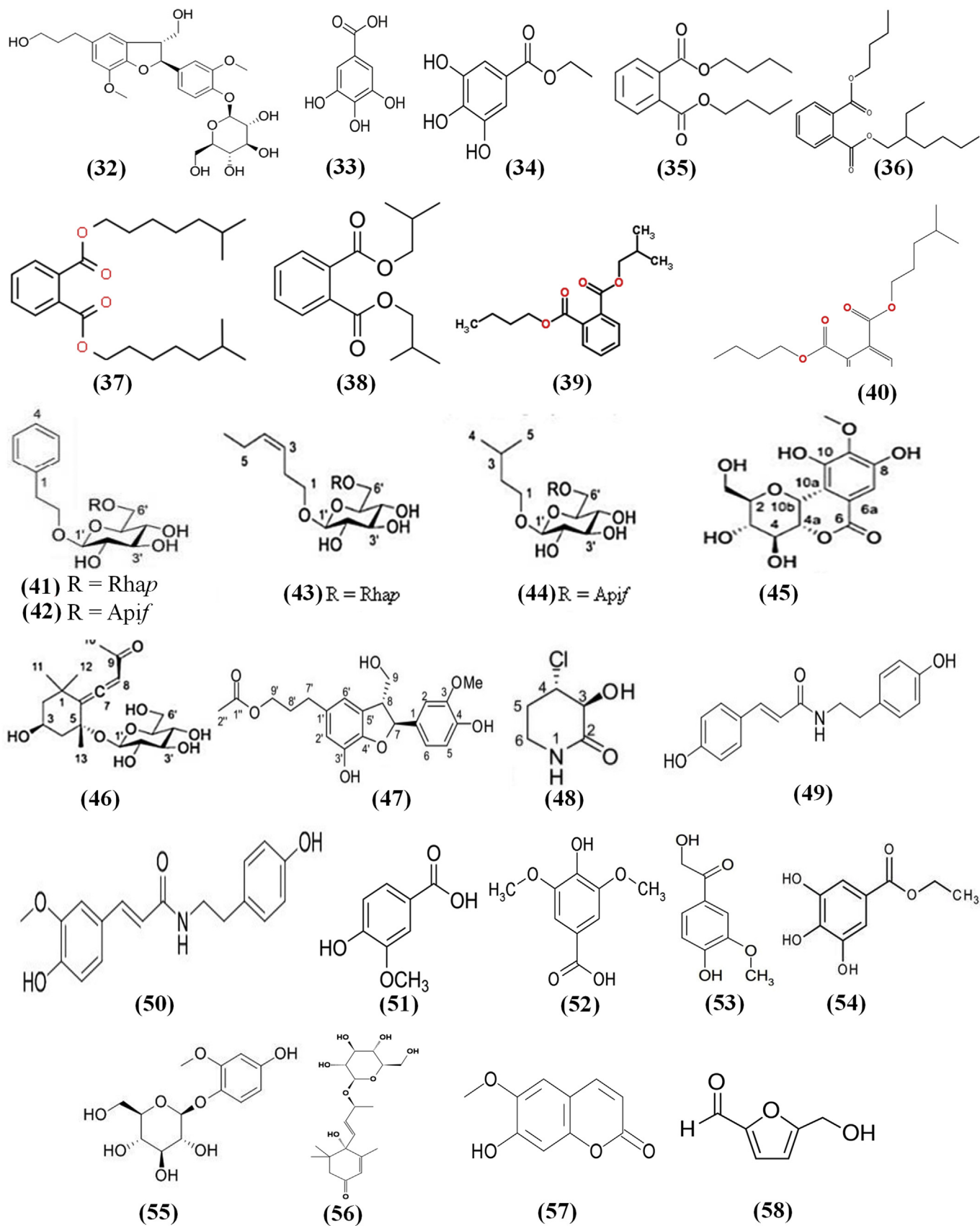


Figure 2. (Continued).

Table 2. A list of chemical compounds isolated from the selected plants of the *Leea* genus with their short descriptions.

Chemical Groups	Compounds Isolated Or Identified	Brief Description	Reference
Steroid	Steroids	The presence of steroids was confirmed from ethanolic extract of <i>Leea indica</i> leaves	[46]
	Steroids	Steroids were identified from hexane, chloroform, ethyl acetate, butanol and aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]
	Stigmasterol (1)	Stigmasterol was isolated from ethanolic extract of <i>Leea macrophylla</i> roots	[50]
Terpenoid	Oleanolic acid (2), Ursolic acid (3), Maslinic acid (4), Chebuloside ii (5), Corosolic acid (6), Hederagenin-3-O-arabinopyranoside (7), Oleanolic acid 3-O- glucopyranosyl-(1→2) - arabinopyranoside (8)	Triterpenoids were identified from methanolic extract of aerial parts of <i>Leea asiatica</i>	[35]
	Triterpenes	These triterpenes were isolated from methanolic extract of <i>Leea asiatica</i>	[37]
	Oleanolic acid (2) & derivatives	These compounds were identified from ethanolic extract of <i>Leea macrophylla</i> roots	[50]
	Terpenoids	These terpenoids were identified from ethanolic extract of <i>Leea indica</i> leaves	[51]
Flavonoid	Quercitrin (9), (+)-Catechin (10), (–) - Epicatechin (11), (–)-Epiafzelechin(12), Juglanin (13), Mearnsin 3-O-rhamnopyranoside (14), Myricitrin (15), Afzelin (16)	These flavonoids were identified from methanolic extract of aerial parts of <i>Leea asiatica</i>	[35]
	Flavonoids	These flavonoids were identified from methanolic extract of <i>Leea asiatica</i>	[37]
	Flavonoids	The presence of flavonoids was confirmed from ethanolic extract of <i>Leea indica</i> leaves	[46]
	Flavonoids	Flavonoids were identified from hexane, acetone, methanol and ethanolic extract of <i>Leea guineensis</i> leaves	[47]
	Quercitrin (9), Quercetin (17), Quercetin-3'-sulphate-3-O- α-L-rhamnopyranoside (18), Quercetin-3,3'-disulphate (19), Quercetin-3,3',4'-trisulphate (20)	These flavonoids were isolated from leaves of <i>Leea guineense</i>	[48]
	Flavonoids	The presence of flavonoids was confirmed from chloroform, ethyl acetate, butanol and aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]
Glycoside	Glycosides	These glycosides were identified from methanolic extract of <i>Leea asiatica</i>	[37]
	Astragaln (21), Isorhamnetin 3-O-β-D-glucopyranoside (22), Isoquercitrin (23), Mauritianin (24)	These flavonoid glycosides were isolated from the ethanolic extract of the of <i>Leea aequata</i>	[39]
	Glycosides	The presence of glycosides was identified from ethanolic extract of <i>Leea indica</i> leaves	[46]
	Glycosides	The presence of Glycosides was confirmed from ethyl acetate, butanol and aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]
	Glycosides	Glycosides were identified from ethyl acetate and methanol extract of <i>Leea macrophylla</i> seeds	[52]
	Mollic acid α-L-arabinoside (25), Mollic acid β-D-xyloside (26)	These glycosidic compounds were isolated from ethyl acetate fraction of <i>Leea indica</i> leaves	[53]
Cardiac Glycoside	Cardiac glycosides	These cardiac glycosides were identified from hexane, acetone, methanol and ethanolic extract of <i>Leea guineensis</i> leaves	[47]
	Cardiac glycosides	These cardiac glycosides were identified from ethanolic extract of <i>Leea indica</i> leaves	[51]
Phenolic Compound	4-hydroxyphenol-[6-O-(4''-hydroxy-3'',5''-dimethoxybenzoate)]-β-D-glucopyranoside (27), Breynioside A (28)	These phenolic glucosides were identified from methanolic extract of aerial parts of <i>Leea asiatica</i>	[35]
	9'-O-acetylisolariciresinol (29), (+)-Lariciresinol (30), (+)-Syringaresinol (31), Urolignoside (32)	These five lignans were isolated from the ethanolic extract of the aerial parts of <i>Leea aequata</i>	[39]
	Gallic acid (33), Ethyl gallate (34)	These phenolic compounds were isolated from leaves of <i>Leea guineense</i>	[48]
	Phenolics	These phenolic compounds were identified from butanol and aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]
	Phenolics	These phenolic compounds were identified from ethyl acetate and methanol extract of <i>Leea macrophylla</i> seeds	[52]
	Tannin	Tannins	The presence of tannins were confirmed from ethanolic extract of <i>Leea indica</i> leaves
Tannin	Tannins	Tannins were identified from hexane, chloroform, methanol and ethanolic extract of <i>Leea guineensis</i> leaves	[47]
	Tannins	Tannins were reported in the butanol and aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]

(continued on next page)

Table 2 (continued)

Chemical Groups	Compounds Isolated Or Identified	Brief Description	Reference
Alkaloid	Alkaloids	The presence of alkaloids was confirmed from aqueous extract of <i>Leea guineensis</i> leaves	[45]
	Alkaloids	The presence of alkaloids was confirmed from ethanolic extract of <i>Leea indica</i> leaves	[46]
	Alkaloids	Alkaloids were reported from hexane, acetone, chloroform, methanol and ethanolic extract of <i>Leea guineensis</i> leaves	[47]
	Alkaloids	These alkaloids were identified from ethyl acetate, butanol and aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]
Saponin	Saponins	The presence of saponins was ascertained from aqueous extract of <i>Leea guineensis</i> leaves	[45]
	Saponins	The presence of saponins was proved from hexane, acetone and ethanolic extract of <i>Leea guineensis</i> leaves	[47]
	Saponins	The presence of saponins was confirmed in the aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]
	Saponins	These saponins were identified from ethanolic extract of <i>Leea indica</i> leaves	[51]
	Saponins	The presence of saponins was showed in n-hexane and chloroform extract of <i>Leea macrophylla</i> seeds	[52]
Essential Oil	di-n-butyl phthalate (35), Butyl-2-ethylhexyl phthalate (36), Isooctyl phthalate (37)	The presence of these oils identified from 1-butanol fraction of methanolic extract of <i>Leea indica</i> leaves	[54]
	di-n-butylphthalate (35), di-isobutylphthalate (38), n-butylisobutylphthalate (39), Butylisohexylphthalate (40)	These essential oils were isolated from diethyl ether extract of <i>Leea indica</i> flowers	[55]
Sugar	Reducing Sugars	These reducing sugars were identified from aqueous extract of <i>Leea guineensis</i> leaves	[45]
	Sugars	These sugars were identified from ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]
	Reducing sugars	The presence of reducing sugar was confirmed from ethanolic extract of <i>Leea macrophylla</i> leaves	[56]
Protein	Proteins	The presence of proteins was confirmed from butanol and aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]
	Proteins	The presence of proteins was confirmed from ethyl acetate and methanol extract of <i>Leea macrophylla</i> seeds	[52]
Carbohydrate	Carbohydrates	The presence of these compounds was identified from ethanolic extract of <i>Leea indica</i> leaves	[51]
	Carbohydrates	The presence of carbohydrates was confirmed from ethyl acetate and methanol extract of <i>Leea macrophylla</i> seeds	[52]
Others	Phenylethyl-rutinoside (41), Icariside D1 (42), Hexenyl-rutinoside (43), Everlastoside C (44)	These diglycosidic compounds were identified from methanolic extract of aerial parts of <i>Leea asiatica</i>	[35]
	Bergenin (45), Citroside A (46)	These compounds were identified from methanolic extract of aerial parts of <i>Leea asiatica</i>	[35]
	(7S,8R)-9'-O-acetylcedrusin (47), (3S,4S)-4-chloro-3-hydroxypiperidin-2-one (48)	These compounds were isolated from the ethanolic extract of the aerial parts of <i>Leea aequata</i>	[39]
	trans-N-p-coumaroyltyramine (49), N-trans-feruloyltyramine (50), Vanillic acid (51), Syringic acid (52), α -hydroxyacetovanillone (53), 3,4,5-trihydroxybenzoic acid ethyl ester (54), Isotachioside (55), (6S,9S)-roseoside C (56), Scopoletin (57), 5-hydroxymethylfurfural (58)	These compounds were isolated from the ethanolic extract of the aerial parts of <i>Leea aequata</i>	[39]
	Amino Acids, Mucilage's	These compounds were identified from aqueous fraction of ethanolic extract of <i>Leea macrophylla</i> root tubers	[49]

fracture, allergy, diarrhoea, dysentery, ulcer, skin diseases, diabetes, wound, sexual disorder, tetanus, piles, paralysis, typhoid, healing cut injury, cancer, gangrene, fever, etc. [12, 13, 14], which ensure the usefulness of *Leea* species for the betterment of peoples' health. Roots and leaves are predominantly used as decoction. A short description of the traditional uses of the *Leea* species available in Bangladesh is shown in Table 1.

3. Bioactive compounds

The genus *Leea* belongs to the Vitaceae family is a very large family having a large number of medicinal plants. Therefore, it is difficult to carry out a detailed chemical literature review of all the plants belong to this family. Due to this shortcoming, an extensive chemical review of the *Leea* plants available in Bangladesh was carried out and claimed to possess mainly flavonoids, glycosides, phenols, terpenoids, steroids,

volatile oils, alkaloids, tannins, saponins, and many other organic compounds [46, 47, 48] (Figure 2, Table 2). These phytoconstituents are well known to produce many pharmacological activities, which is the evidence of the importance of this genus. A short description of the detailed chemical literature review of *Leea* genus is shown in Table 2.

4. Pharmacological activity

Pharmacological activity is the capacity of a specific molecular entity (drug) to achieve a defined biological effect (beneficial or adverse effect) on a living body [57]. Plants are the most important source of drugs. Around 25% of the prescribed drugs worldwide are derived from plants [58], which revealed the pharmacological importance of plant compounds. The Vitaceae family is rich in medicinal plants having a folkloric reputation to cure different ailments. Various reported biological data about the plants of *Leea* genus suggest that the plants have different

pharmacological activities. It is quite impractical to perform a detailed biological review of all plants belong to this genus. Therefore, a detailed biological review of the selected plants of the genus *Leea* available in Bangladesh was carried out using different search engines to explore the pharmacological potentials found in these species.

4.1. Antimicrobial activity

Antimicrobial activity may be defined as the process of destroying or inhibiting the growth of pathogenic microorganisms [59]. There are different types of antimicrobial agents such as antibacterial, antiviral, antifungal, antiprotazoal, etc. that are used to kill or inhibit the growth of microorganisms.

4.1.1. Antibacterial activity

The ethyl acetate extract of *Leea rubra* root was reported to have a significant antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* [42]. The ethanolic extract of *Leea macrophylla* root tubers showed a wide range of antibacterial activity against both Gram-positive and Gram-negative bacteria [49]. The n-hexane, chloroform, ethyl acetate, and methanol extracts of *Leea macrophylla* seed were effective against *Staphylococcus aureus* [52]. The essential oil of *Leea indica* flowers showed strong antibacterial activity against *Escherichia coli* and *Salmonella typhimurium* and moderate activity against *Bacillus subtilis*, *Bacillus cereus*, and *Staphylococcus aureus* [55]. The dichloromethane extract of *Leea indica* stems exhibited significant activity against *Staphylococcus epidermis* and *Staphylococcus aureus* [60]. A separate study stated that the extracts of seed, stem and root of *Leea aequata* were reported to have antibacterial activity against *Bacillus anthracis*, *Bacillus pumilis*, *Salmonella paratyphi*, *Staphylococcus albus*, *X. compestris*, and *X. malvacearum* [61]. All these reported data indicate that *Leea* plants have antibacterial potentials and could be equally effective against other microorganisms like fungi, virus, etc.

4.1.2. Antifungal activity

The ethanolic extract of *Leea indica* leaves exhibited antifungal activity against *Candida albicans*, *Aspergillus flavus*, and *Fusarium equisetii* due to the presence of flavonoids and steroids [46]. The ethyl acetate, methanol and chloroform extracts of *Leea macrophylla* seed were shown to exhibit antifungal activity against *Candida albicans* [52]. The essential oil extracted from *Leea indica* flowers showed strong activity against *Penicillium notatum* and moderate activity against *Aspergillus niger* and *Fusarium monelliformae* [55]. Tareq et al., (2017) demonstrated antifungal activity of methanolic extracts of *Leea indica* and *Leea macrophylla* leaves against a number of fungi such as *Candida albicans*, *Blastomyces dermatitidis*, *Aspergillus niger*, *Pityrosporum ovale*, *Microsporum spp.*, *Trichophyton spp.*, and *Cryptococcus neoformans* [62]. These results indicate that the species of *Leea* genus are important sources for a diverse range of antifungal metabolites.

4.1.3. Antiviral activity

The agents that kill virus or suppress its ability to replicate followed by inhibiting its ability to multiply and reproduce are known as antiviral agents [63]. It was reported that the ethanolic extract of *Leea indica* leaves exhibited antiviral activity against HSV-1 (herpes simplex virus type-1) [64].

4.1.4. Anthelmintic activity

Anthelmintics are a group of antiparasitic drugs that expel parasitic worms (helminths) and other internal parasites from the intestine by either stunning or killing them without causing significant damage to the host [65]. The methanolic extract of *Leea asiatica* leaves was shown to exhibit effectiveness against Indian adult earthworms (*Pheretima posthuma*) [66] suggesting the potential source of *Leea asiatica* as an anthelmintic.

4.1.5. Antimalarial activity

Malaria is a serious and life threatening disease caused by *Plasmodium* parasites that are transmitted to humans through the bites of infected *Anopheles mosquitoes* [67]. Generally, malaria is treated with the prescription drugs. However, Sulistyarningsih et al., (2017) demonstrated the antimalarial activity of the methanolic extract of *Leea indica* leaves in malaria-induced mice model [68]. This result may give an indication that other species of *Leea* genus could have antimalarial potentials.

4.2. Antioxidant activity

Oxidation is a chain of chemical reactions that produces free radicals, thereby leading to damage the living cells of organisms. Antioxidants are substances that inhibit oxidation [69]. Antioxidants play vital role in maintaining good health of human being and preserving foods by protecting cellular materials such as DNA and lipid in the body from oxidation. It was reported that the methanolic extract of *Leea asiatica* leaves possessed significant antioxidant activity by increasing the levels of endogenous antioxidant enzymes [36]. The extract of *Leea aequata* leaves showed a moderate antioxidant effect, which was confirmed by scavenging the DPPH free radicals [40]. The ethanolic extract of root of *Leea rubra* has potent radical scavenging activity [42]. Previous two studies reported that the ethanolic extract and its different fractions of *Leea macrophylla* root tubers were reported to have potential antioxidant activity [49, 50]. The water and methanolic extracts of *Leea indica* leaves exhibited significant antioxidant activity [70, 71]. These *in vitro* and *in vivo* reported data indicate that *Leea* species are an important source of natural antioxidants that can suppose to prevent cell damage by preventing or scavenging free radicals and by improving the levels of endogenous antioxidant enzymes.

4.3. Cytotoxic activity

The cytotoxicity is the quality of being toxic to cells. Cytotoxic drugs prevent or inhibit the function of cells [72]. Exposing cells to a cytotoxic compound may result in a variety of cell fates. The cells may undergo necrosis in which they lose membrane integrity and die rapidly due to cell lysis. Cytotoxic drugs are drugs used to destroy cancer cells. Cytotoxic drugs inhibit cell division, thereby leading to die of cancer cells. Two previous studies stated that the ethanolic and methanolic extracts of *Leea indica* leaves exhibited cytotoxic activity in experimental models [73, 74]. In another study, it was reported that the ethanolic extract of *Leea macrophylla* roots showed preliminary cytotoxic activity [75]. These results together suggest that the *Leea* plants might show a potential anticancer activity.

4.4. Anticancer activity

Cancer is defined as a disease in which a group of cells grow uncontrollably and rapidly by disregarding the normal rules of cell division. It is noted that cancer develops when the body loses its own control mechanism, leading to conversion of normal cells into cancer cells [76]. Anticancer activity is the activity of an agent or substance against cancer. The agent may be a natural or synthetic or chemical substance that can reverse, suppress or prevent carcinogenic progression. There are many *in vitro* and *in vivo* methods that are considered to estimate anticancer properties of natural products. More than 80% of existing anticancer drugs were derived from plants. Like wise, the mollic acid α -L-arabino-side and mollic acid β -D-xyloside of *Leea indica* leaves showed cytotoxic effect on CaSki (cervical cancer) cells [53]. The methanol, ethanol and aqueous extracts of *Leea indica* leaves exerted *in vitro* growth inhibitory effect against two prostate cancer cell lines (DU-145 and PC-3) [71]. A separate study conducted by Rainah et al., (2012) reported that the methanolic extract of the leaves of *Leea indica* showed antitumor activity against Ehrlich Ascites Carcinoma cells in Swiss albino mice [77]. As these plants were effective against several types of cancers, it can be said

that the unexplored plants of this genus may introduce a new era of cancer treatment in the future.

4.5. Antidiabetic activity

Diabetes is a metabolic disorder caused by the body's inability to produce or respond to the pancreatic hormone insulin, leading to a high level of glucose in blood. Antidiabetic activity is the ability of a drug to lower the increased blood glucose by increasing entry of glucose into cells and by increasing the activity of insulin [78]. The ethanolic extract of *Leea indica* leaves reduced blood glucose and lipid levels, indicating its efficient antihyperglycemic and hypolipidemic activities [51]. In another study, it was found that the ethanolic extract of *Leea macrophylla* leaves showed a potential effort to restore pancreatic β -cell damaged in streptozotocin-induced albino rats [79] suggest that the *Leea* species could be a new source of antidiabetic agents.

4.6. Wound healing activity

The wound is an injury to the body that typically involves laceration or breaking of a membrane and usually damage to the underlying tissues. Wounds that are more difficult to heal include delayed acute wounds and chronic wounds. There are four phases of wound healing: hemostasis, inflammation, proliferation, and remodeling. Healing a wound properly and timely, all the four phases of healing should be done sequentially and appropriately [80]. The methanolic extract of aerial parts of *Leea asiatica* showed significant wound healing effects [37]. Moreover, the ethanolic extract of *Leea macrophylla* root tubers produced significant wound healing [81]. According to these findings, it can be stated that *Leea* species may provide a good scope of research for wound healing activity.

4.7. Anti-inflammatory activities

Anti-inflammatory activity is defined as the ability of a drug to reduce inflammation (redness, swelling, and pain) in the body. Anti-inflammatory agents block certain substances in the body that cause inflammation [82]. Some anti-inflammatory agents are being studied in the prevention and treatment of cancer. Nair et al., (2014) reported that the methanolic extract of *Leea asiatica* exhibited potent anti-inflammatory effect [37]. In another study, the ethanolic extract of *Leea macrophylla* leaves showed significant *in vitro* anti-inflammatory activity by inhibiting the denaturation of egg albumin [56]. These data represent the anti-inflammatory potential of *Leea* species.

4.8. Central nervous system (CNS) activity

CNS depressants slow normal brain functions. In higher doses, some CNS depressants can become general anesthetics. On the other hand, CNS stimulants stimulate the brain through speeding up both mental and physical processes [83]. The methanolic extract of *Leea indica* leaves showed potent sedative and anti-anxiety activities [84]. The methanolic extract of *Leea macrophylla* root exerted neuroprotective activity on diazepam-induced memory impairment in amnesic Wistar albino rat [85]. The CNS activity is one of the most important pharmacological activities of these plants, which requires more research in this sector.

4.9. Hepatoprotective activity

Hepatotoxicity means liver damage or injury caused by chemicals called hepatotoxins. Hepatoprotection or antihepatotoxicity is the ability of a drug to prevent damage to the liver. Plant extracts can be the best source of antihepatotoxic and mediate hepatoprotective activity. The methanolic extract of *Leea asiatica* leaves produced hepatoprotective activity by lowering the level of serum SGOT, SGPT, ALP, total bilirubin, total cholesterol and triglyceride in acetaminophen-induced experimental model [36]. An *in vivo* study conducted by Ajiboye et al., (2014)

stated that the aqueous seed extract of *Leea guineensis* showed hepatoprotective activity against DDVP-induced oxidative stress by altering the levels of increased lipid peroxidation and enhancing decreased activities of antioxidative enzymes such as catalase, superoxide dismutase, and glutathione peroxidase [43]. In another study, it was found that the methanolic extract of *Leea macrophylla* leaves partially improved the hepatic damage in CCl₄-induced Wistar albino rats and prevented oxidative damage as well [86]. Therefore, it might be considered that the reported pharmacological activities of the plants of *Leea* genus indicate their wide variety of protective activity of liver.

4.10. Antipyretic activity

Anti means against and pyretic means feverish. Thus an antipyretic is a substance that reduces fever [87]. Most of the antipyretics work by inhibiting the enzyme cyclooxygenase and by reducing the levels of PGE₂ within the hypothalamus. Antipyretics cause the hypothalamus to override a prostaglandin-induced increase in temperature [88]. The body then works to lower the temperature, which results in a reduction in fever. The methanolic extract of *Leea rubra* roots reduced fever induced by yeast suggested that the plant has antipyretic effect [89]. The other plants of *Leea* genus might have potent antipyretic activity, as *Leea rubra* showed.

4.11. Anticonvulsant activity

Anticonvulsant activity of a drug is to prevent or reduce the severity of epileptic attacks or to arrest dangerous muscle contraction in electroconvulsive therapy. Anticonvulsants generally work by calming hyperactivity in the brain in various ways. These drugs are used in seizures, migraine, and other brain disorders [90]. Woode et al., (2011) reported that the aqueous extract of *Leea guineensis* leaves showed anticonvulsant activity [44]. The ethyl acetate fraction of *Leea aequata* leaves showed anticonvulsant effects on the colon contraction induced by acetylcholine [91]. In another study, it was reported that the ethanolic extract of *Leea aequata* leaves showed a significant relaxation activity against the smooth muscle contraction of isolated guinea pig trachea induced by acetylcholine [92].

4.12. Thrombolytic activity

The thrombolytic activity of a drug is defined as the ability to dissolve dangerous clots in blood vessels, improve blood flow, and prevent damage to tissues and organs. Thrombolytic agents are used to treat a heart attack, stroke, deep vein thrombosis, pulmonary embolism, and occlusion of peripheral artery or indwelling catheter [93]. These agents work by converting plasminogen to plasmin, which breaks down the fibrinogen to fibrin and thus dissolve the clot. It was reported that the methanolic extract of *Leea indica* leaves showed moderate thrombolytic effect [94] suggests that other plants belong to *Leea* genus might have such activity and need to do further study to explore their activity.

4.13. Antiedematogenic activity

Edema is a swelling due to excess accumulation of fluid in the intercellular tissue that results from an abnormal expansion in interstitial fluid volume [95]. Edematogenic causes edematous swellings and anti-edematogenic inhibit the edematous swellings. An *in vivo* study stated that the aqueous extract of *Leea guineensis* leaves showed anti-edematogenic activity in carrageenan-induced rat paw edema model in mice [45].

4.14. Anti-nociceptive and Anxiolytic Activity

Anti-nociception is the process or action of blocking the detection of a painful or injurious stimulus by sensory neurons. Anti-nociceptive agents

are the substances that inhibit nociception (the sensation of pain). Anxiolytic agent inhibits anxiety (an emotion characterized by feelings of tension) and anxious thoughts and reduces high blood pressure. Like diazepam, the aqueous extract of *Leea guineensis* leaves exhibited dose-dependent anti-nociceptive and anxiolytic activities [44]. The ethanolic extracts of roots of *Leea macrophylla* exerted anti-nociceptive activity [76]. These results indicate that other plants of this genus might show anti-nociceptive and anxiolytic activities.

4.15. Antidiarrhoeal activity

Antidiarrheal drugs are drugs that relieve the symptoms of diarrhea and the frequent passage of a watery stool. The methanolic extract of *Leea indica* and *Leea macrophylla* leaves exhibited anti-diarrheal activity by reducing stool volume in mice [62]. This data suggests that the *Leea* species may provide a good source of antidiarrheal agents.

4.16. Antiuroliathic activity

Urolithiasis is the formation of stones (calculi) in the urinary tract. It is one of the most common urinary tract diseases. Antiuroliathic agents dissolve or prevent the formation of urinary calculi. *Leea* species might have shown significant antiuroliathic activity, as *Leea macrophylla* extract reduced and prevented the growth of kidney stones and improved the renal impairment in the ethylene glycol-induced urolithiatic model in rats [96].

5. Conclusion

In this review, a general view of the previous research on the species of the *Leea* genus has been summarized and focused to outline the information regarding the traditional uses, bioactive phytochemicals and pharmacological potentials of the *Leea* plants. The *Leea* genus contains around 70 species, which are widely used as TM in many countries, including Bangladesh due to their therapeutic potentials in various ailments or disorders such as diabetes, diarrhea, wounds, inflammation, hepatotoxicity, neural disorders, cancer, renal impairments and microbial infections. Moreover, several phytochemicals such as alkaloids, terpenoids, flavonoids, tannins, steroids, glycosides, phenolics, proteins and carbohydrates present in these plants are shown to exhibit pharmacological activities justify the use of these plants as TM. Only a few of the species of *Leea* genus have been investigated for their chemical constituents and pharmacological activities. Hence, there are enormous scopes for further scientific investigation to establish *Leea* plants as a potential source of novel drugs.

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Author contribution statement

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