Journal of
Materials in Life Sciences

Vol. 3 No. 1 (2024)

Full Paper

Phytochemical Attributes and Pharmacological Activities of Genus Leucas: A Mini Review

Muhammad Luqman Selahuddeen[a], Noor Aida Fazira Mohd Salleh[a], Lee Fui Lin[a], Hemagirri Manisekaran[b], Marouane Dhia Eddine Bouguerra[c], Wan Nur Aqilah Wan Mohd Samsudin[a], Siti Ernieyanti Hashim[a], Roswanira Abdul Wahab[a], Abdul Fatah A. Samad[b], Faizuan Abdullah[a,*]

[a] Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia.
[b] Department of Biosciences, Faculty of Science, 81310 Universiti Teknologi Malaysia (UTM), Johor Bahru, Johor.
[c] Department of Agri-Food, Environmental and Animal Sciences, University of Udine, Via Sondrio 2A, 33100 Udine, Italy.

Article history
Received
22 August 2023
Revised
13 May 2024
Accepted
14 May 2024
Published online
30 May 2024

*Corresponding author
faizuan@utm.my

Abstract

The *genus Leucas* is among the plethora of ethnobotanical species with promising applications in traditional medicines to treat different ailments. Despite extensive studies on the *Leucas genus*, the focus has largely been on their ethnobotanical importance alongside a modest number of studies on their phytochemical- or pharmacological attributes, including but not limited to antibacterial, anti-inflammatory and anthelmintic. In this review, phytochemical data alongside pharmacological activities of several notable species in the *Leucas genus* are compiled. The review focuses on the chemical constituents and essential oils that several species from this genus produce. Previous studies on the prominent species of this genus reported the presence of many beneficial chemical constituents, such as flavonoids, phenols, tannins, and alkaloids, that are substantial to the genus's pharmacological activities. However, these studies are preliminary in the sense that the proven in vitro activities are not further studied on the molecular level, efficacy, toxicity, and clinical levels. Insight into the pharmacological activities are discussed in this review: anthelmintic, anti-microbial, anti-inflammatory, antioxidant, anti-diarrheal, anti-diabetic, and anti-nociceptive alongside hepato-protective activities. The lack of extensive in vivo studies but the immense medicinal potential is viewed as an opportunity for further studies on the genus.

Keywords *Genus Leucas,* medicinal plant, phytochemical study, pharmacological activities, ethno botanical

1.0 INTRODUCTION

Medicinal plants have been widely used by humans to treat various health issues since ancient times (Kumar and Devanna, 2016). Each country would have a different range of traditional medicinal plant species locally grown in their surroundings. India has abundant traditional medicinal plants, a source of formidable and powerful drugs (Rupani and Chavez, 2018). In fact, herbal plants are essential in traditional medicine. Even in modern-day society, rural and sometimes urban communities use such plants in their daily lives. Exploration into the medicinal values of natural plants is being focused on as an alternative to synthetic medications. Biological activities in phytochemicals exist mainly for the plants' inherent need for protection against attacks from microorganisms, insects and herbivorous animals (Behl et al., 2021; Fernandez-Conradi et al., 2021; Sharma et al., 2021).

This review aims to collect and narrate the studies that have been done on the genus Leucas, from its many species spread across Asia and Africa to the phytochemical compounds found in these plants and the similarities between species or distinct compounds found in only a few. We also gather the pharmacological activities of these plants and try to bring light to future works that may be paramount in the field of pharmacology. Plant phytochemicals comprise naturally occurring primary and secondary metabolites. Primary metabolites, *viz*. carbohydrates, lipids and proteins, are involved directly in plants' growth and metabolic pathway. Secondary metabolites, such as alkaloids, phenolics, steroids, sterols, lignins, tannins, etc., are the end products of primary metabolism and do not partake in metabolic activity. By uncovering the different phytoconstituents' biological activity, synthetic chemists could create larger quantities of the compounds and subsequently treat human health problems (Patil et al., 2019; Sharma et al., 2021). Herbal plants are undeniably an important source of important phytochemicals, which explains their extensive use in different industries such as food, pharmaceutical, and cosmetics (Saito, 2018; Zahra et al., 2020).

The genus Leucas of the Lamiaceae family, consisting of more than 200 plant species, is widely distributed in the tropical regions of southern Africa, Taiwan, Japan, Arabian Peninsula, Iran to South China, Southeast Asia, and down to Australia (Harley et al., 2004, Zielinska and Matkowski, 2014). However, most studies on the genus Leucas depict only the Asian species, while the Afro-Arabian species was assigned an informal name, the 'African Leucas' (Scheen and Albert, 2009). The plants are normally annual- or perennial shrubs, sub-shrubs, woody roots and/or stem bases. Interestingly, the oval-shaped, tapered end leaves have petiolate whole or spiky lobes and are occasionally found without the main stalk (Ryding, 1998). Nearly 63% of the Leucas species are native to India (Sunojkumar and Mathew, 2008), and the diversity increases towards the Southern parts of the country. In fact, the Leucas species has always been the main herbal medicine in Ayurveda, Homeopathy, as well as Siddha, and Unani (Khare, 2007).

Leucas plants can grow in low and high-altitude habitats along seacoasts, roadsides, near wetlands, grasslands, scrub jungles, and rocky hills. Studies have shown that the plant extracts have antioxidant, anti-microbial, analgesic, anti-inflammatory, anti-diarrheal and insecticidal properties (Chouhan and Singh, 2011; Kulkarni et al., 2013; Meghashri et al., 2010). These properties could be ascribed to a large number of phytoconstituents present in the Leucas species. Among the constituents include lignans, coumarins, steroids, flavonoids, terpenes, lactone, leucasin, aliphatic ketols, fatty acids, leucasone, aliphatic long-chain compounds, coumarleucasin, flavone, diterpenes and essential oil compounds (Chouhan and Singh, 2011; Al Yousuf et al., 1999; Misra et al., 1992; Hasan et al., 1991; Pradhan et al., 1990; Sadhu et al., 2006; Moody et al., 2006; Khalil et al., 1996).

For instance, the *Leucas aspera* has pharmacological activities that comprise antioxidant, analgesic, anti-microbial, insecticidal, anti-fungal, anti-pyretic, anti-inflammatory, and anti-diarrheal properties (Nirmala and Kanchana, 2018). Likewise, *Leucas indica* was extensively utilized to treat psoriasis, painful swellings, chronic skin eruptions, jaundice, asthma, fever and cold, and inflammation. The plant extract expedites wound healing and treats dyspepsia, scorpion stings, and snake bites (Babu et al., 2018). Similarly, the *Leucas martinicensis* effectively reduces inflammation, skin rashes, convulsions, kidney disorders, diarrhea, epilepsy, fever, cough and rheumatism (Minja, 1999; Agra et al., 2007; Ugwah-Oguejiofor et al., 2015). Equally, the small, earthy, non-woody *Leucas zeylanica* is called the Ceylon slitwort, a hispid aromatic plant with oval-shaped leaves that grows to 120 cm in height (Radhika et al., 2018). The *L. zeylanica* leaves have stimulant and sedative, and diaphoretic properties. Aside from promoting wound healing, the leaf extract was used for treating itchiness, headaches, scabies, soreness of eyes and nostrils, jaundice, burning, and urination issues (Jayaweera, 1982; Khandelwal et al., 2003; Hossain et al., 2013). The ethnopharmacological use of *L. zeylanica* was reported by Napagoda et al. (2018) for anti-inflammatory and anti-gout remedies. Additionally, Abdullah et al. (2019) first reported that *L. zeylanica* exhibited antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*.

2.0 Phytochemical aspects of Leucas species

Literature on the phytochemical aspects of the Leucas genus has been found to include these five *Leucas* species *viz. Leucas cephalotes*, *Leucas aspera*, *Leucas lavandulaefolia, Leucas mollissima,* and *Leucas zeylanica*. These species have an abundance of secondary metabolites comprising terpenoids, flavonoids, alkaloids, lactones, phenolic compounds and phenylpropanoids. Table 1 enlists the chemical compounds isolated from the *Leucas* species and while Figure 1 depicts their chemical structures.

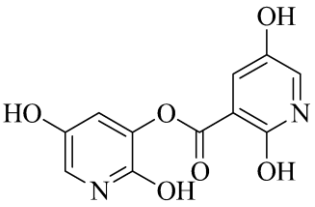
Table 1. Chemical compounds isolated from the genus of *Leucas*

Compounds Extracted for Medicinal Used	Species	Part	Reference
2′,5′-dihydroxy-3′-pyridyl-(2,5-dihydroxy) pyridinyl-3-carboxylate **1**	*L. cephalotes*	Flower	(Priya et al., 2019)

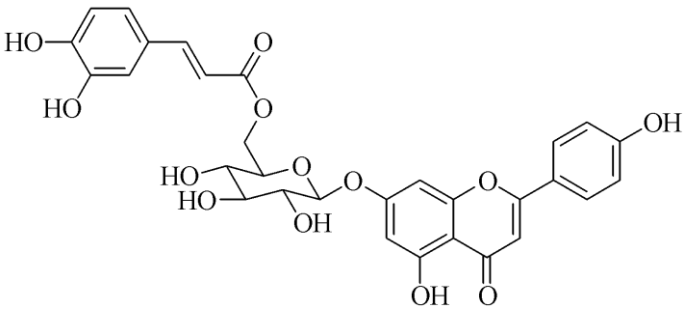
Apigenin-7-O-(6''-O-E-caffeoyl)-β-D-glucopyranoside **2**	*L. aspera*	Flower	(Manivannan, 2016)
Acacetin **3** Chrysoeriol **4** Luteolin **5** Acacetin 7-O-β-D-glucuronide **6** Acetoside **7** Isoacetoside **8** Salicylic acid **9** Caffeic acid **10**	*L. lavandulaefolia*	Stem	(Begum et al., 2015)
(−)*epi*-marmelo lactone **11** Schensianol A **12** Vanillin **13** β-Hydroxy propiovanillone **14** Lanost-9(11),25-diene-3β,24β-diol **15** Lanost-9(11),23E(24)-diene-3β,25-diol **16** (+) syringaresinol **17** Anisofolin A **18** Apigenin 7-O-β-D-(-6″-p-E-coumaroyl)-glucoside **19**	*L. mollissima*	Aerial parts	(Chinchansure et al., 2015)
Leucasinoside **20** 19-O-β-D-carboxyglucopyranosyl-12-O-β-D-glucopyranosyl-11, 16-dihydroxyabieta-8, 11, 13-triene **21** 12,19-O-β-D-diglucopyranosyl-11,16-dihydroxyabieta-8, 11, 13-triene **22**	*L. zeylanica*	Aerial parts	(Zhang et al., 2016)
Leuctriterpencoside **23** (–)-epiloliolide **24** (E)-4- ((1S,3R,4R)-1-hydroxy-4,5,5-trimethyl- 7-oxabicyclo [4.1.0]heptan-1-yl)but-1-en-3-one **25**	*L. zeylanica*	Stem	(Chen et al., 2019)
Adenica **26** 6*β*-Acetoxy-9*α*,13-epoxy-16-norlabd-13*E*-en-15-al **27** Apigenin-7-*O*-(6″-*E*-p-coumaroyl)-*β*-D-glucopyranoside **19** Torosaflavone A **28** Drymariatin C **29** Daidzein **30** luteolin 3′,4′-dimethyl ether **31** Apigenin **32** Tricin **33** Chrysoeriol **4** Linarigenin **34** *β*-sitosterol **35** Stigmasterol **36** Ethyl caffate **37** Evofolin B **38** Dibutylphthalate **39** Dibutylterephthalate **40** Tyrosol **41** Catechol **42** Dehydrovomifoliol **43**	*L. zeylanica*	Whole plant	(Nidhal et al. 2020; Chinchansure et al., 2015; Begum et al., 2015)

Cucumegastigmanes I **44**
Loliolide **45**
Isololiolide **46**
4-hydroxyphthalide **47**
Ethyl-D-galactopyranoside **48**
Uracil **49**
L-phenylalanine **50**
Aurantiamide acetate **51**
1H-indole-3-carbaldehyde **52**
cytochalasin H **53**

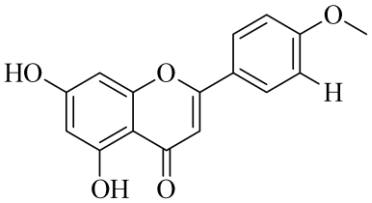
According to the information of compounds extracted from the *Leucas* genus in Table 1, and their parts, it showed that *L. zeylanica* is the species that has been investigated wholly to be studied, while other species are only studied in parts whether just flower or aerial parts. The researchers discovered a new abietane diterpenoid glycoside: leucasinoside **20,** alongside two other known compounds, namely the 19-*O*-*β*-D-carboxyglucopyranosyl-12-*O*-*β*-D-glucopyranosyl-11,16-dihydroxyabieta-8,11,13-triene **21** and 12, 19-O-β-D-diglucopyranosyl-11, 16-dihydroxyabieta-8, 11, 13-triene **22** (Zhang et al., 2016). Additionally, the ethanolic extract of the stem revealed a new triterpenoid glucoside: leuctriterpencoside **23,** together with two known compounds, (–)-epiloliolide **24** and (*E*)-4- (1S,3R,4R)-1-hydroxy-4,5,5-trimethyl-7-oxabicycloheptan-1-yl)but-1-en-3-one **25** (Chen et al., 2019). A recent study by (Nidhal et al. 2020) isolated thirty compounds from the whole plant of *L. zeylanica,* which include a new compound and 29 known compounds. Two norditerpenoids: adenica **26** and 6*β*-Acetoxy-9*α*,13-epoxy-16-norlabd-13*E*-en-15-al **27**, three flavonoid glycosides: apigenin-7-*O*-(6″-*E*-p-coumaroyl)-*β*-D-glucopyranoside **19**, torosaflavone A **28** and drymariatin C **29**. Among others, six flavonoids: daidzein **30**, luteolin 3′,4′-dimethyl ether **31**, apigenin **32**, tricin **33**, chrysoeriol **4** and linarigenin **34**, two phytosterols: *β*-sitosterol **35** and stigmasterol **36**, two phenylpropanoids: ethyl caffate **37** and evofolin B **38**, were identified. Additionally, two phthalate esters: dibutylphthalate **39** and dibutylterephthalate **40**, two phenolic compounds: tyrosol **41** and catechol **42**, were discovered. A total of five terpenoids: dehydrovomifoliol **43**, cucumegastigmanes **44**, loliolide **45**, isololiolide **46** and 4-hydroxyphthalide **47**, were found alongside an aliphatic glycoside: ethyl-D-galactopyranoside **48**, as well as a nucleobase, uracil **49**. The amino acid, *L*-phenylalanine **50**, two alkaloids: aurantiamide acetate **51** and 1H-indole-3-carbaldehyde **52**, and finally a cytochalsin: cytochalasin H **53**, were also isolated from the plant. All compounds were found for the first time from *L. zeylanica*. In all, the isolated compounds **26**, **27**, **29-32**, **37-53** were all assigned to the Lamiaceae family (Nidhal et al., 2020).



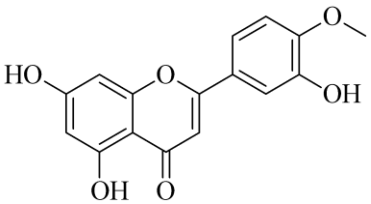
1



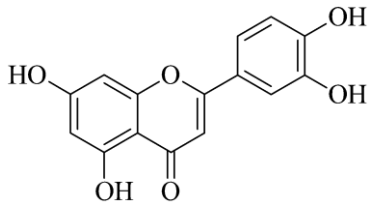
2



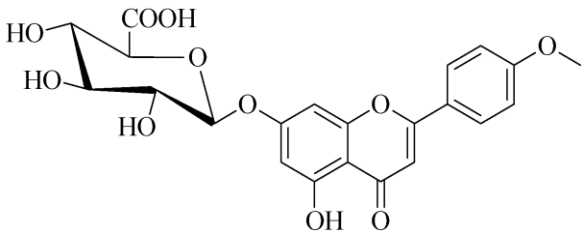
3



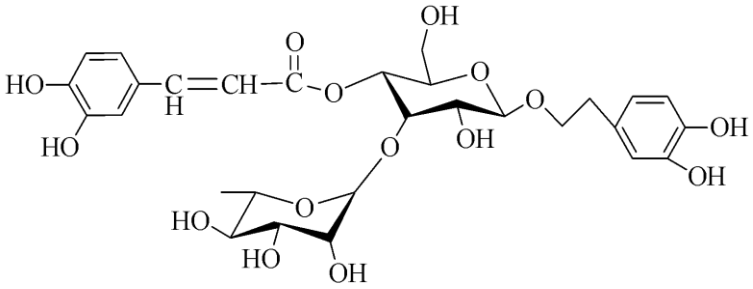
4



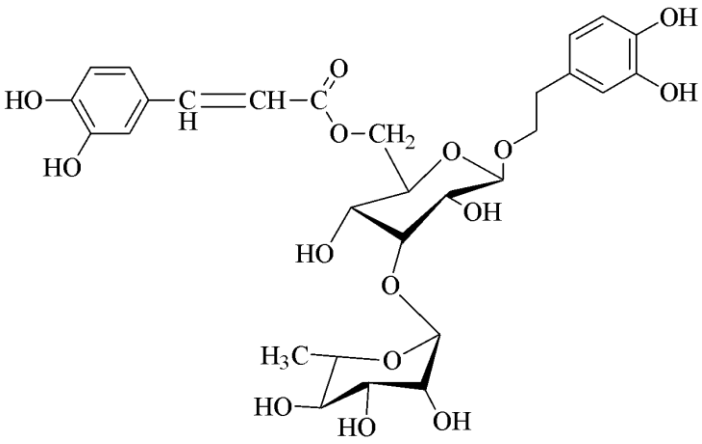
5



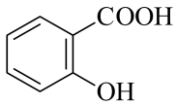
6



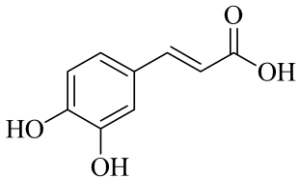
7



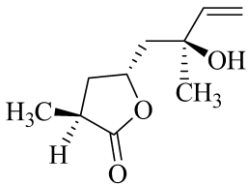
8



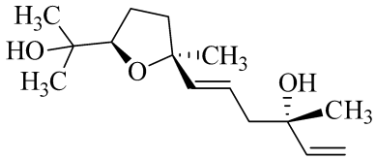
9



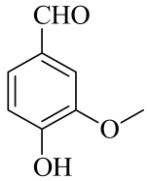
10



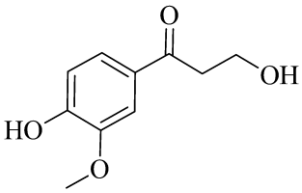
11



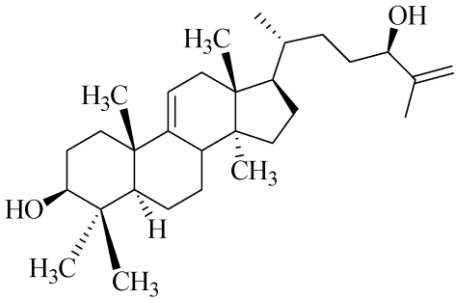
12



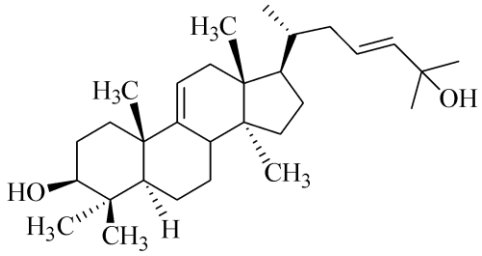
13



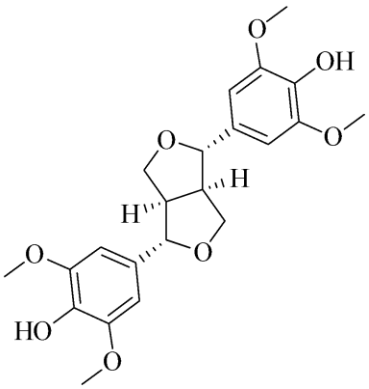
14



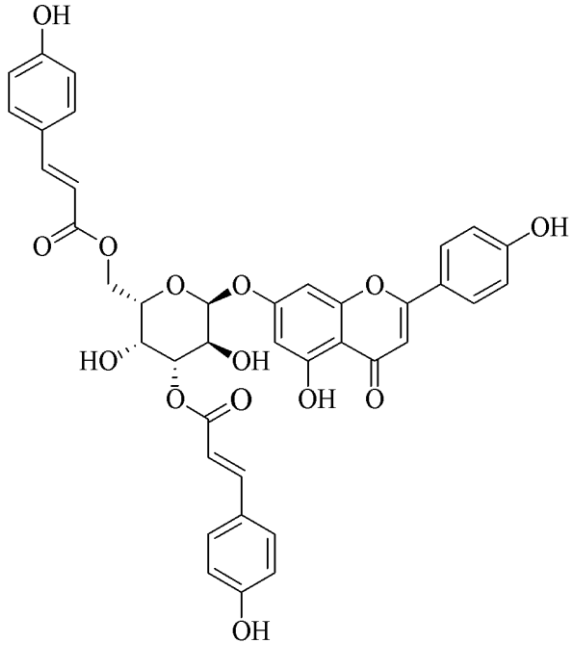
15



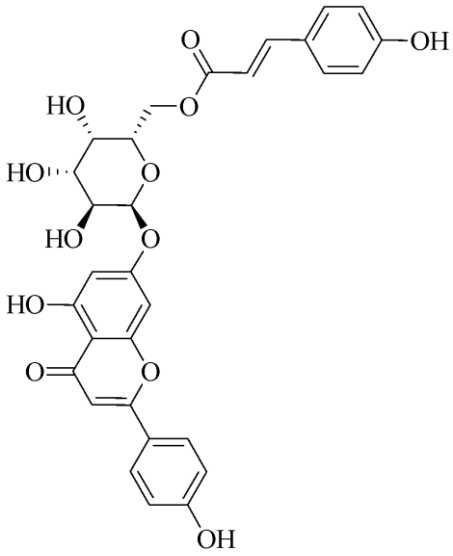
16



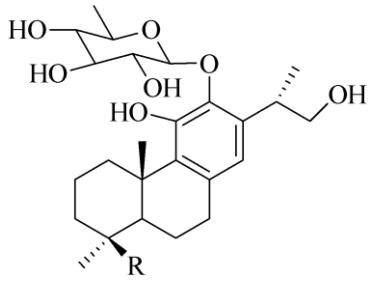
17



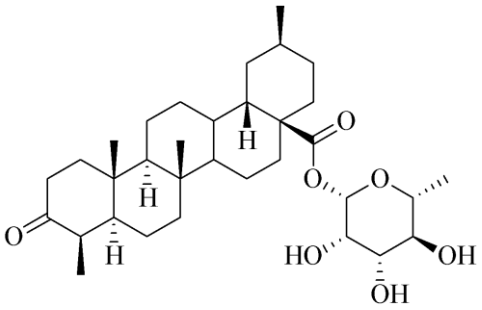
18



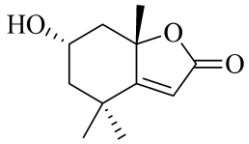
19



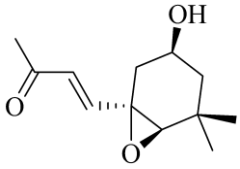
20 R=COOH
21 R=COOglc
22 R=CH_2Oglc



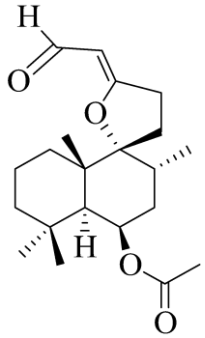
23



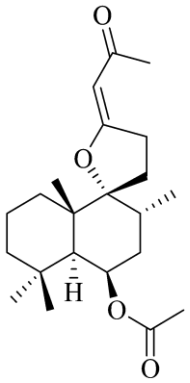
24



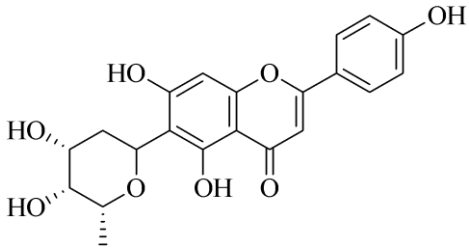
25



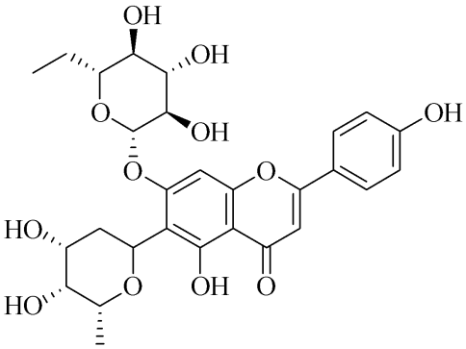
26



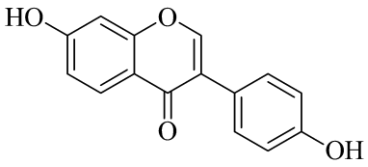
27



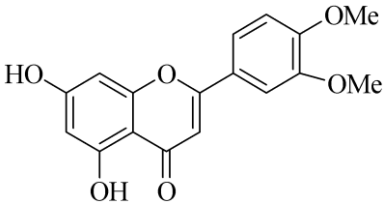
28



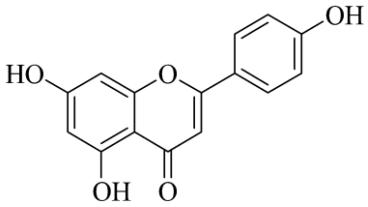
29



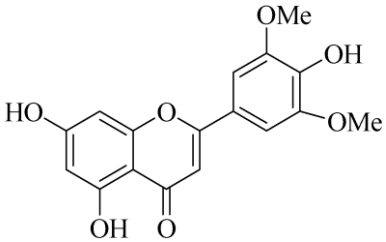
30



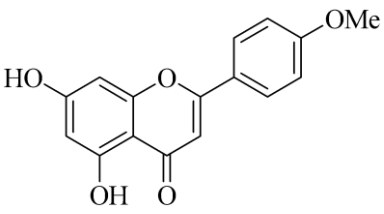
31



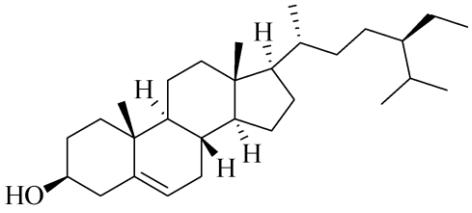
32



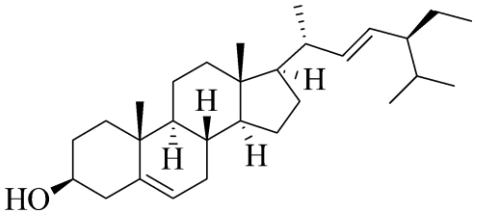
33



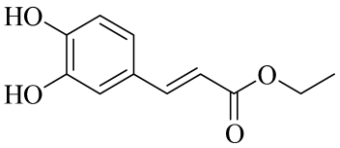
34



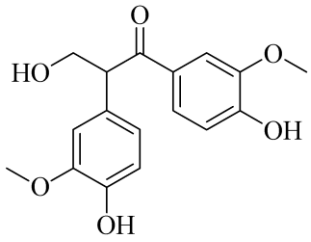
35



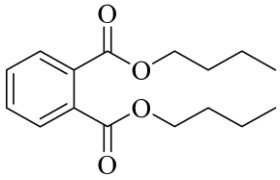
36



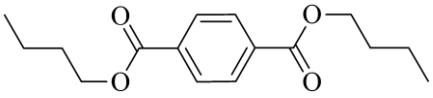
37



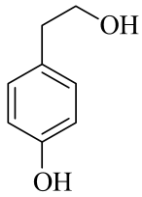
38



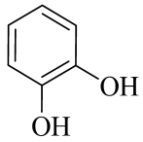
39



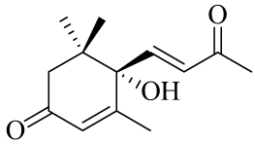
40



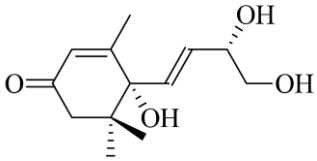
41



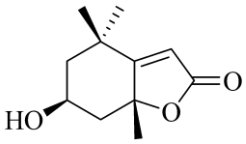
42



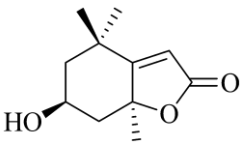
43



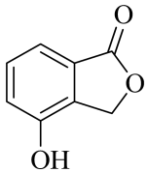
44



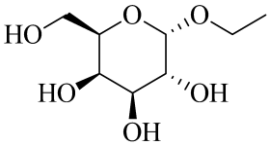
45



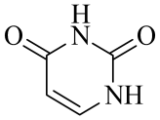
46



47



48



49

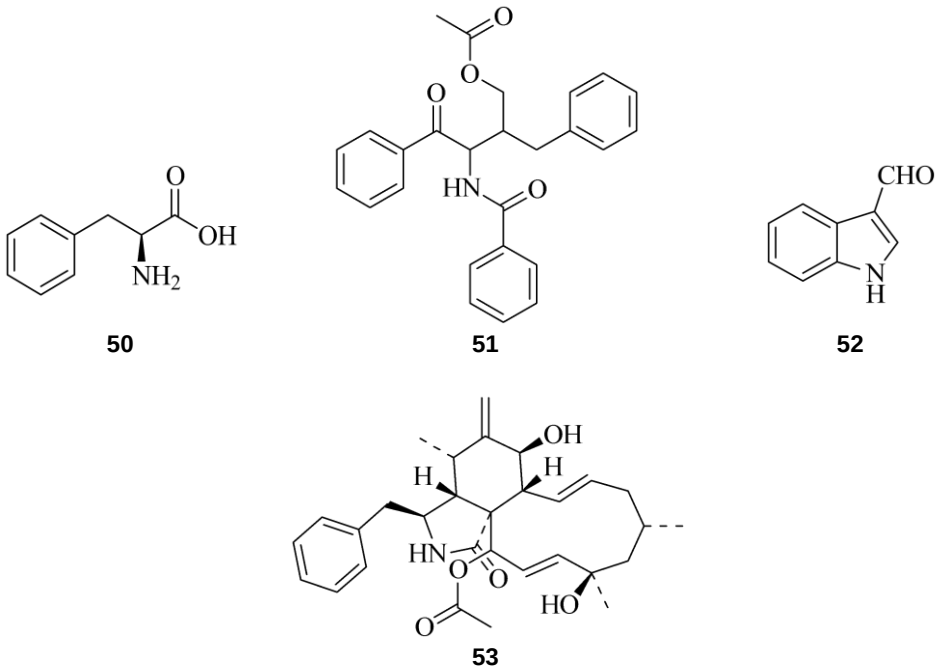


Figure 1. Chemical structures of the isolated compounds from the genus *Leucas.*

3.0 Essential Oils produced by the Genus *Leucas*

Literature survey showed that a few studies on essential oils of *Leucas* species have been conducted (Joshi, 2015; Moody, 2006; Joshi, 2014). In these studies, it has been found that the essential oils from the Leucas genus to be antifungal, anticancer, antimicrobial, can act as local anesthetic and also other peripheral effects (Joshi, 2015; Mothana et al., 2017). The chemical composition of the essential oils of ten species of *Leucas*: *Leucas mollissima*, *Leucas inflata*, *Leucas aspera*, *Leucas deflexa*, *Leucas glabrata*, *Leucas indica*, *Leucas martinicensis*, *Leucas milanjiana*, *Leucas virgata* and *Leucas zeylanica* are reported and the major constituents are shown in **Table 2**.

Table 2. Major Constituents of Genus *Leucas* Essential Oils.

Species	Locality	Major constituents	Reference
L. mollissima	India	**Aerial parts:** Germacrene D (16.0 %), alencene (15.6 %), β-caryophyllene (14.9%), bicyclo-germacrene (8.5 %), β-phellandrene (6.0 %) and ρ-cymene (4.6 %)	(Prasad et al., 2017)
L. inflata	Yemen	**Flowering aerial parts:** Hexadecanoic acid (32.8%), *n*-dodecanoic acid (7.8%), camphor (6.1%), and linalool (3.2%)	(Mothana et al., 2017)
L. aspera	India	**Aerial parts:** β-caryophyllene (34.2%), 1-octen-3-ol (14.8%), α-humulene (6.3%), α-pinene (5.8%), epi-α-bisabolol (4.6%) and limonene (4.5%)	(Joshi et al., 2015)
	Nepal	**Aerial parts:** 1-octen-3-ol (30.6%), caryophyllene oxide (24.4%), (E)-caryophyllene (23.4%), (E)-nerolidol (9.4%), α-humulene (6.4%) and β-eudesmol (5.7%)	(Satyal et al., 2012)

L. indica	India	**Aerial parts:** β-caryophyllene (51.1%), α-caryophyllene (10.2%), limonene (3.5%), terpinolene (3.5%), caryophyllene oxide (1.8%), cembrene (1.7%), 14-hydroxy-(Z)-caryophyllene (1.5%), and totarene (1.5%)	(Joshi et al., 2014)
L. virgata	Yemen	**Aerial parts:** Camphor (20.5%), β-eudesmol (6.1%), fenchone (5.4%), caryophyllene oxide (5.1%), exo-fenchol (3.4%) and borneol (3.1%)	(Mothana et al., 2013)
L. zeylanica	Vietnam	**Aerials parts:** β-caryophyllene (21.4-25.5%), α-humulene (8.4-9.8%), germacrene D (2.8-14.6%), β-Selinene (9.3-11.9%), 1-tetradecanol (7.8-9.3%) and phytol (5.3-9.8%)	(Hung et al., 2019)

In a previous work, essential oils from the aerial parts of *L. mollissima* Wall. ex Benth which grows in the Himalayan region of Uttarakhand, India, was found to be rich in sesquiterpene hydrocarbons (64.1%) and monoterpene hydrocarbons (13.7%) (Prasad et al., 2017). Conversely, the essential oils of the *L. inflata* Balf.f. has an abundance of aliphatic acids (51.1%), followed by oxygenated monoterpenes (16.0%) (Mothana et al., 2017). The essential oils of the *L. aspera* (Willd.) Link. collected in the Northwest Karnataka region of India reportedly has a high amount of sesquiterpene hydrocarbons (47.7%), which differed substantially from essential oils extracted from parts of Leucas species growing in Nepal (Joshi, 2015). Comparison of essential oils extracted from the same Leucas species growing in India and Nepal showed an interesting revelation. The major components in the *L. aspera* leaf and flower essential oils of the Indian species were absent in plants growing in Nepal. It again demonstrates that different geographical locations and climates can impact the chemical composition of essential oils from the same plant species (Satyal et al., 2012).

In another study, the *L. indica* (L.) R.Br. is found to be rich in sesquiterpene hydrocarbons (71.8%). *L. martinicensis* (Jacq.) R.Br. from Rwanda also contained a high amount of sesquiterpene hydrocarbons in its oil. The essential oil of *L. virgata* Balf.f. was found to possess a high content of oxygenated monoterpenes (50.8%) (Mothana et al., 2013). From the data obtained, it can be concluded that many essential oils *Leucas* species are rich in sesquiterpene hydrocarbons. Furthermore, germacrene D, β-caryophyllene and α-humulene were the major constituents found in the essential oils of many *Leucas* species.

4.0 Pharmacological activity of genus *Leucas*

4.1 Anti-inflammatory activity

Inflammation is a self-defence response of our body to various hazardous stimuli. However, an uncontrolled response leads to a continuum of disorders, including allergies, cardiovascular dysfunction, metabolic syndrome, cancer, and autoimmune diseases. The therapeutic anti-inflammatory effects in certain medicinal plants could reduce the inflammation response with the lowest degree of unwanted adverse effects (Ghasemian et al., 2016). *L. aspera* was reported to exhibit a high anti-inflammatory effect by blocking and inhibiting IL-1β, an important pro-inflammatory cytokine produced by activated macrophages. Moreover, a recent mouse macrophage cell line RAW264.7 study by Nagarajan et al. (2019) showed that the dried powder plant extracts a whole *L. aspera* plant resulted in a progressively elevated cytokine inhibition from 24 % to 39 % when tested between 250−1000 ug/ml of the plant extract, showing that the extract can be considered as the cytokine inhibitor. Similarly, anti-inflammatory action in the aqueous and methanolic extracts of the *L. aspera* leaves was also reported through a series of tests involving lipoxygenase inhibition, albumin denaturation- and membrane stabilization assay, and proteinase inhibitory activity at inhibitory concentrations, the IC_{50} value of 356.3 µg/ml, 249.6 µg/ml, 206.7 µg/ml, 206.7 µg/ml and 421.6 µg/ml, respectively (Tahareen et al., 2016).

Likewise, the *L. cephalotes* (Roth.) Spreng extract, which was done by dichloromethane extraction (LCD), was tested on female Sprague Dawley rats for *in vivo* inhibition of pro-inflammatory cytokines (Patel et al., 2015). It was revealed that 50 mg/kg, 100 mg/kg and 400 mg/kg doses of the extract significantly reduced TNF-α levels in test subjects by 1340 µg/ml, 1045 µg/ml and 673 µg/ml and IL-1β levels by 889 µg/ml, 697 µg/ml and 481 µg/mL, respectively. Additionally, new abietane diterpenoid glycoside, leucasinoside, alongside two known compounds from aerial parts of *Leucas zeylanica* (L.) R. Brown

potently reduced inflammation (Zhang et al., 2016). The lipopolysaccharide-induced nitric oxide production test results on RAW264.7 macrophages showed moderate inhibition, with IC_{50} values between 12.6−18.8 μM (Zhang et al., 2016).

In another study using *L. vestita*, the anti-inflammatory effect of the aqueous ethanolic plant extract was tested in Wistar rats administered with 0.1 ml of 1% W/V of carrageenan solution on the rats' paws. In this study, positive control was made with rats receiving a 10 mg/kg b dose. wt. p.o indomethacin and 2 test groups of rats that receive 200 mg/kg b. wt. p.o and 400 mg/kg b. wt. p.o of plant extract (Rajesh et al., 2021). The results show that the plant extract inhibitory response to the carrageenan is comparable to indomethacin, although dose-dependent as 10 mg/kg b. wt. p.o of indomethacin inhibits up to 7% while 400 mg/kg b. wt. p.o of plant extract inhibits 6%. The study also denotes that the mechanism of action of the plant extract's anti-inflammatory is similar to that of indomethacin by blocking prostaglandin and thromboxane formation via inhibition of cyclo-oxygenase and arachidonic acid. The plant extract contains phytosterols that can modify the prostaglandin pathway and flavonoids that inhibit prostaglandin synthetase (Rajesh et al., 2021). By using molecular modelling, they determined that phenolic compounds gallic acid, ferulic acid, caffeic acid, quercetin, and rutin played major roles in the docking and bonding activity to the Cyclo-oxygenase 2 model, which concluded that the action against this Cyclo-oxygenase 2 enzyme by the active compounds could eliminate pain. Other researchers like Spiegel (1983) and Katzung (1992) also concluded the same result as Rajesh et al. (2021). However, this study only proved the docking simulation, and the real anti-inflammatory test should be performed for an accurate and proven result.

L. chinensis was also studied for its anti-inflammatory effects. It was found that this plant ethanolic extract works by inhibiting lipopolysaccharide–triggered pro-inflammatory cytokines and mediators (Wu et al., 2020). In this study against RAW264.7 cells, *L. chinensis* extract of 0.2 mg/ml inhibited nitric oxide production by 84%, nitric oxide being the signaling molecule of inflammations.

4.2 Anti-microbial activity

The anti-microbial property in the extracts of the *Leucas* plant has potential use for treating bacterial and fungi-related diseases. For instance, the anti-microbial potential of petroleum ether and chloroform extracts of the *L. marrubioides* Desf. root was discovered to be highly effective against the majority Gram-positive (*Streptococcus pyogenes, Staphylococcus epidermidis* and *Bacillus subtilis*), Gram-negative bacteria (*Proteus mirabilis, Klebsiella pneumoniae* and *Vibrio cholerae*) and fungal strains (*Cryptococcus neoformans, Curvularia* sp. and *Candida albicans*). The petroleum ether and chloroform Leucas extracts were assessed for their anti-microbial properties, revealed the lowest minimum inhibitory concentration (MIC) of 1.562 mg/ml against *Vibrio cholerae* and 1.562 mg/ml for the *Curvularia* species (Gowrish et al., 2016).

Additionally, anti-microbial activities of the dichloromethane (DCM) leaf extracts of *L. aspera* (Willd.) L. were observed on selected microbes at 1 mg/disc, 2.5 mg/disc, 5 mg/disc and 10 mg/disc concentrations. The MIC of the DCM leaf extract was found to be in the range of 75.5−425.5 μg/ml against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Pseudomonas vulgaris,* and *Klebsiella pneumonia* and 125 μg/ml to 425 μg/ml against *Trichoderma viride*, *Candida albicans*, *Aspergillus flavus* and *Epidermophyton floccosum* for anti-fungal activities (Pavunraj et al., 2017). Similarly, the anti-microbial activity of *L. cephalotes* Spreng. was also affirmed against bacterial strains.

The MIC of the ethanolic extract of *L. cephalotes* Spreng was 250 μg/ml against *Staphylococcus aureus*, *Escherichia coli* and *Vibrio cholera* and 500 μg/ml against two fungal strains *viz*. *Candida albicans* and *Aspergillus niger*, respectively (Jangra et al., 2016). However, the ethanolic extract of the Leucas species comparatively imparts a stronger anti-microbial activity than the aqueous extract (Jangra et al., 2016). Likewise, the methanolic leaf extract of *L. zeylanica* exhibited appreciable anti-fungal activity on the agar well diffusion test (Babu et al., 2016), which showed the extract producing a 5−10 mm zone of inhibition. The maximum was recorded against *Penicillium* sp. (10 mm), and the minimum was against *Candida tropicalis* (3 mm) (Babu et al., 2016). Comparably, the anti-microbial activity of the *L. lanata* Wall. ex Benth. was more effective against bacterial strains compared to fungal ones. The 50 % ethanolic extract of the 200 μg/disc produced a maximum inhibition zone against Gram-positive bacteria *Staphylococcus epidermidis* (20.2 – 21.5), alongside Gram-negative bacteria *Salmonella typhi* (20.3 – 20.9) and *Salmonella typhimurium* (20.1 – 19.4). The recorded corresponding inhibition zones were between 17.1 – 18.5 mm and 15.5−17.5 mm against *Candida krusei* and *Aspergillus fumigatus*, respectively (Dixit et al., 2015).

4.3 Antioxidant activity

Phytochemicals of the *Leucas* genus could scavenge the free radicals that may harm and contribute to various diseases (Kaur and Kumar, 2016). For the antioxidant capacity test, the anti-oxidative strength of the *L. marrubioides* Desf. extracts were evaluated using extraction in different solvents, namely, petroleum ether, chloroform and methanol. Then, the antioxidant potential of each extract was assessed by DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging assay and nitric oxide scavenging assay, and reducing power was assessed with Ferric reducing method (Gowrish et al., 2015). Results revealed that the methanolic extract showed the highest antioxidant activity for all models, achieving IC_{50} values of 245.3 μg/ml, 335.33 μg/ml and 575.8 μg/ml, respectively, than the moderate activity by pet ether and chloroform. The antioxidant activity recorded by this

study was likely contributed by the abundance of flavonoids, phenolics, and other phytoconstituents in the extracts (Gowrish et al., 2015).

Another study explored the petroleum ether leaf extract of *L. aspera* (Willd) using in vitro models (Annapandian and Rajagopal, 2017) and found that non-polar solvent extracts exhibited stronger antioxidant activity. This was apparent in the IC_{50} value of 18.96 µg/ml in the DPPH assay, and the total anti-oxidant assay and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) assay yielded the corresponding 17.22 µg/ml, 16.00 µg/ml and 11.87 µg/ml. Conversely, the polar solvents plant extracts, namely the ethanolic extracts, yielded the best antioxidant activity with IC_{50} values of 19.90 µg/ml, 13.47 µg/ml and 11.60 µg/ml, respectively (Annapandian and Rajagopal, 2017).

Besides, the *L. aspera* methanolic leaves extract exhibited an appreciable antioxidant activity with a corresponding IC_{50} value for DPPH radical scavenging activity at 20 µg/ml compared to 9.34 µg/ml in the standard (ascorbic acid) (Kaur and Kumar, 2016). Likewise, the nitric oxide and free radical scavenging assay of the 10 µl, 50 µl and 100 µl of *L. aspera* flower extracts demonstrated 50.27%, 69.73%, 82.70% and 15.33%, 30.6 % and 57.26% antioxidant capacities, respectively (Sabri and Vimala, 2018).

4.4 Anthelmintic activity

The crude methanolic extract of *L. lavandulifolia* is a well-recognized anthelmintic medicinal plant in Bangladesh. This fact has been proven using earthworms as a test model. A previous study indicated that the crude plant extract exhibited profound anthelmintic activity against earthworms in a dose-dependent manner for concentrations ranging from 10−50 mg/ml (Islam et al., 2017). Similarly, Kalpana et al. (2016) found that the aqueous crude extract of *L. aspera* displayed a significant anthelmintic effect on adult Indian earthworms, which resembles the parasitic intestinal roundworm in humans. The worms were killed when 5 mg/ml, 25 mg/ml, 50 mg/ml and 100 mg/ml of the extracts were used in the investigation. However, the duration of the onset of paralysis and death were noticeably varied between 34−64 minutes and 42−70 minutes (Kalpana and Rajeswari, 2016). Interestingly, tannins in the crude leaves extract affected the degrees of helminthiasis in each extract. The study noticed that tannins interfered with energy generation in helminth parasites, killing them in the process (Kalpana and Rajeswari, 2016).

Meanwhile, anthelmintic properties were also assessed for the *L. indica* extracts using earthworms as the model. The methanolic extract of the plant was quick to paralyze the earthworms within 9.3 min, 6.5 min and 4.5 min, when the corresponding 10 mg/ml, 25 mg/ml and 50 mg/ml concentrations were utilized. Their findings proved that the *L. indica* extracts showed promising anthelmintic treatment applications (Babu et al., 2018).

4.5 Anti-diarrheal activity

Rahman et al. (2018) reported that 200 mg/kg and 400 mg/kg doses of the *L. cephalotes* ethanolic leaves effectively reduced mortality and inhibited castor oil- and $MgSO_4$-induced diarrheal test in mice. However, the 400 mg/kg extracts exhibited stronger, anti-diarrheal activity than the 200 mg/kg in both models (Rahman et al., 2018). The study attributed the ethanolic plant extracts containing appreciable amounts of tannins and flavonoids, contributing to the reduced incidence of diarrhea in mice. The above outcome was plausibly due to increased electrolyte and water re-absorption from the gastrointestinal tract (Rahman et al., 2018). The same observation was also reported for the *L. chinensis* leaf extract (Hase et al., 2016). Equally, the ethanolic extract of the aerial part of *L. lavandulaefolia* led to a notable decrease in the emergence and severity of diarrhea in castor oil-induced diarrhea in rats (Chouhan and Singh, 2011). Likewise, *L. martinicensis* is also popular among certain Ugandan tribes as an anti-diarrheal agent (Ramalingam and Ravinder, 2013).

4.6 Hepato-protective activity

The liver is susceptible to injury, i.e., hepatotoxicity, especially chronic, prolonged exposure to drugs *viz.* paracetamol, acetaminophen, environmental toxicants and xenobiotics like carbon tetrachloride (CCl_4), all of which could lead to serious health problems (Hashemid et al., 2019). Hepato-protective or anti-hepatotoxicity are compounds with an activity that prevents liver damage caused by hepatotoxic agents (Shamsi-Baghbanan et al., 2014).

Scientists explored the hepato-protective activity of orally administered paracetamol-induced hepatoxicity. Methanolic extracts of *L. aspera* roots (200 mg/kg, 400 mg/kg and 800 mg/kg) *in vivo* in rats, and found that the extracts' protective effects were comparable to the standard, Silymarin (25mg/kg b.w). The 400 mg/kg b.w and 800 mg/kg b.w of *L. aspera* methanolic root extracts-treated rats exhibited significant hepato-protective activity, respectively. This activity gauged based on serum levels of biochemical parameters *viz.* the Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Alkaline Phosphatase (ALKP), Total Bilirubin (TBL), Total Cholesterol (CHL), Total Protein (TPTN) and Albumin (ALB) (Kamble and Ganga Rao, 2017). The *L. aspera* extract treatments decreased SGOT, SGPT, ALKP, TBL, and CHL levels while elevated levels of TPTN and ALB. These favorable changes were pertinent in preventing hepatocellular damage and biliary obstruction leading to necrosis in the liver (Kamble and Ganga Rao, 2017).

The *L. cephalotes* ethanolic extracts were also evaluated by a recent study for hepatoprotective activity. Results revealed that a 600 mg/kg dose effectively protected the liver against 3 gm/kg paracetamol-induced injury, proving the hepatoprotective activity of the extracts (Islam et al., 2020). In contrast, an earlier study reported a lower dose (200 mg/kg and 400 mg/kg) of the alcoholic extracts of *L. cephalotes* showed an appreciable hepato-protective effect in isoniazid and rifampicin (100 mg/kg)-induced hepatoxicity in Sprague Dawley rats (Bais and Saiju, 2014). The alcoholic extracts' hepato-protective effect manifested by increased superoxide dismutase activity and glutathione and catalase levels while decreasing SGPT, SGOT, ALKP levels and other biomarkers (Bais and Saiju, 2014).

4.7 Antinociceptive activity

Plants of the *Leucas* genus are also known for their anti-nociceptive properties. The phytochemicals have valuable pain-relieving properties, with little or no side effects, by blocking stimuli from sensory neurons that detect pain or injury (Mannan et al., 2019). Previously, swiss albino mice orally administered with the methanolic extract of *L. aspera* (250 mg/kg, 500 mg/kg and 700 mg/kg) were tested for six different pain models (hot plate-, tail immersion-, acetic acid-induced writhing-, formalin-induced paw licking-, glutamate-induced nociception- and cinnamaldehyde-induced nociception. The 700 mg/kg dose exhibited the most significant anti-nociceptive activity for all tested pain models, especially in the hot plate and tail immersion tests. Likewise, corresponding inhibitions of 82.74%, 72.35% and 84.74% were observed for the writhing-, early phase formalin-, and licking tests in the late phase (Mannan et al., 2019).

Moreover, in the glutamate- and cinnamaldehyde-induced nociception tests, the 700 mg/kg *L. aspera* methanolic extract inhibited licking by 80.96% and 7 %, respectively (Mannan et al., 2019). Meanwhile, the combined aerial parts of *L. aspera* and *Zingiber officinale* rhizome extract successfully reduced writhing in mice due to induced abdominal pain (Nipu et al., 2017) by 65.4%, at the highest dose of 400 mg/kg compared to aspirin. The same aspirin dosage (standard drug) only reduced abdominal writhing by only 50.0% (Nipu et al., 2017).

4.8 Anti-diabetic activity

A study evaluated the *L. aspera* (Willd.) Link leaves polar (ethanol)-, and non-polar (petroleum ether) extracts for anti-diabetic activity using *in vitro* models (Annapandian and Sundaram, 2017). The petroleum ether extract was more cytotoxic on the C2C12 cell line (110.75 µg/ml) than the ethanolic counterpart (415.25 µg/ml), at 50 % of cell growth inhibition. Meanwhile, when tested at the same concentration, the ethanol extract gave better glucose uptake activity in the C2C12 cell line than the petroleum ether extract (Annapandian and Sundaram, 2017). Anti-diabetic evaluations using *L. aspera* leaf extracts on streptozotocin-induced diabetic Wistar albino rats showed that the 200 mg/kg and 400 mg/kg aqueous extracts produced low blood sugar levels at 117.66 mg/dl and 98.35 mg/dl, respectively, from the 4^{th} day onwards. The blood sugar level-reducing effect of the *L. aspera* leaf aqueous extracts continued until the end of treatment (14^{th} day). The extract concentration also showed good hypoglycemic activity than 200 mg/kg and the reference control (Madhu et al., 2019).

Similarly, *in vitro* investigation by α-amylase inhibition on four industrially relevant *L. cristata*, *L. mollissima*, *L. aspera,* and *L. biflora* (based on starch–iodine and 3,5 dinitro salicylic acid methods) revealed the *L. asper* and *L. mollissima* showing exceptional anti-diabetic properties, with corresponding IC_{50} values of 1.56 mg/ml and 0.75 mg/ml, respectively, in both DNS and iodine starch assays (Shukla et al., 2016). The anti-diabetic activity was detected in the *L. cephalotes* fruit and leaves ethanolic extracts by the same assay, with corresponding IC_{50} values of 92.86 µg/ml and 98.09 µg/ml (Verma et al., 2017). The findings affirmed that the extracts showed potential as an alternative treatment for type 2 diabetes mellitus by reducing postprandial hyperglycemia through starch breakdown (Verma et al., 2017).

5.0 Future Outlook and Conclusion

This article encompassed the botanical description, traditional uses, pharmacological activities and the active phytochemicals of Leucas family plants, especially *Leucas zeylanica*. This plant family's origins and regions in which many of its species are found made it susceptible to early discovery as traditional ailments, particularly in Ayurvedic medicine. Described as a shrubby plant growing in abundance, the species showed high potential as a therapeutic agent stemming from its already evident traditional use; however, unfortunately, most of the pharmacological studies conducted were carried out in-vitro and not excessively. To date, no preclinical or clinical studies have been conducted to confirm these activities. Additionally, qualitative and quantitative phytochemical studies were done by isolating monomolecular compounds. Different equipment isolation methods were used to isolate different compounds in different concentrations and singular compounds. These plants revealed therapeutic potentials as anti-inflammatory agents, anti-microbial agents against prominent bacterial cell lines and anthelmintic properties. Further studies must be done to solidify the use of this plant as a natural substitute for chemical drugs for inflammation, parasites and bacterial infections. This article evidenced the huge gap in research on the physiological uses of *L. zeylanica* and its actual commercial application. The lack of in vivo studies on traditional plant remedies poses several significant

implications regarding scientific understanding and public health. Without in vivo studies, it's challenging to determine the true efficacy and safety profile of traditional plant remedies. While some remedies may have been used for generations and have anecdotal evidence supporting their effectiveness, we cannot be certain about their therapeutic benefits or potential risks without rigorous scientific studies. In vivo studies can help identify active compounds, optimize dosage regimens, and uncover potential drug interactions while establishing quality control measures and standardization protocols for traditional plant remedies. By scientifically documenting the efficacy of traditional plant remedies, we can better appreciate and preserve the cultural heritage associated with these practices. The absence of in vivo studies on traditional plant remedies underscores the need for further scientific investigation to validate their therapeutic properties, ensure patient safety, and maximize their potential contributions to healthcare. Future studies must be carried out exploring the efficacy and practicality of using this natural plant as a substitute or replacement for antimicrobial, anti-inflammatory and anthelmintic treatments. Additionally, clinical trials must be held to evaluate *L. zeylanica* extracts' safety and usability for humans.

Acknowledgement

This research was supported by Universiti Teknologi Malaysia under the grant of Research University Grant (RUG) Tier 2 (Q.J130000.2654.16J57).

References

Abdullah, F., Nasir, S. N. A. M., Han, D. K., Appalasamy, S., Nor, M. M., & Rak, A. E. (2019). Potential of *Leucas zeylanica* extract to eliminate *E. coli* and *S. aureus* in *Corbicula fluminea* ("Etak") tissue. *Malaysian Journal of Fundamental and Applied Sciences*, *15*(4), 597-599.

Agra, M. D. F., Freitas, P. F. D., & Barbosa-Filho, J. M. (2007). Synopsis of the plants known as medicinal and poisonous in Northeast of Brazil. *Revista Brasileira de Farmacognosia*, *17*, 114-140.

Al Yousuf, M. H., Bashir, A. K., Blunden, G., Yang, M. H., & Patel, A. V. (1999). Coumarleucasin and Leucasone from *Leucas inflata* Roots. *Phytochemistry*, 95–98.

Annapandian, V. M., & Rajagopal, S. S. (2017). Phytochemical evaluation and in vitro antioxidant activity of various solvent extracts of *Leucas aspera* (Willd.) Link leaves. *Free Radicals and Antioxidants*, *7*(2), 166-171.

Babu, A., Mohamed, M. S. N., Jaikumar, K., Anand, D., & Saravanan, P. (2016). In-vitro antifungal activity of leaf extracts of *Leucas aspera* and *Leucas zeylanica*. *International Journal of Pharmaceutical Sciences and Research*, *7*(2), 752.

Babu, N., Singh, A., & Singh, R. (2018). Therapeutics potential and pharmacological properties of *Leucas indica*: A review. *The Pharma Innovation, 7(*7), 564–568.

Bais, B., & Saiju, P. (2014). Ameliorative effect of *Leucas cephalotes* extract on isoniazid and rifampicin induced hepatotoxicity. *Asian Pacific Journal of Tropical Biomedicine*, *4*, S633-S638.

Begum, P., Wang, Y., & Fugetsu, B., (2015). Biologically active compounds from *Leucas lavandulaefolia*. *International Journal of Pharmaceutical Sciences and Research*, *6*, 1013-1021.

Behl, T., Kumar, K., Brisc, C., Rus, M., Nistor-Cseppento, D.C., Bustea, C., Aron, R.A.C., Pantis, C., Zengin, G., Sehgal, A. and Kaur, R. (2021). Exploring the multifocal role of phytochemicals as immunomodulators. *Biomedicine & Pharmacotherapy*, *133*, 110959.

Chen, G. Y., Zhang, B., Zhao, T., Nidhal, N., Jia-Li, W., Zhou, X. M., & Chun-Yan, D. (2020). A new triterpenoid glucoside from *Leucas zeylanica*. *Natural product research*, *34*(13), 1874-1878.

Chinchansure, A. A., Arkile, M., Shukla, A., Shanmugam, D., Sarkar, D., & Joshi, S. P. (2015). *Leucas mollissima*, a source of bioactive compounds with antimalarial and antimycobacterium activities. *Planta Medica Letters*, *2*(01), e35-e38.

Chouhan, H. S., & Singh, S. K. (2011). A review of plants of genus Leucas. *Journal of Pharmacognosy and Phytotherapy*, *3*(3), 13-26.

Dixit, V., Verma, P., Agnihotri, P., Paliwal, A. K., Rao, C. V., & Husain, T. (2015). Antimicrobial, antioxidant and wound healing properties of *Leucas lanata* Wall. ex Benth. *The Journal of Phytopharmacology*, *4*(1), 9-16.

Fernandez-Conradi, P., Castagneyrol, B., Jactel, H., & Rasmann, S. (2021). Combining phytochemicals and multitrophic interactions to control forest insect pests. *Current Opinion in Insect Science, 44*, 101-106.

Ghasemian, M., Owlia, S., & Owlia, M. B. (2016). Review of anti-inflammatory herbal medicines. *Advances in Pharmacological and Pharmaceutical Sciences*, *2016*.

Gowrish, A., Vagdevi, H. M., & Rajashekar, H. (2016). Phytochemical screening and antimicrobial activity of *Leucas marrubioides* desf. root extracts. *Int J Pharm Pharm Sci*, *8*(12), 209–12.

Gowrish, A., Vagdevi, H. M., & Rajashekar, H. (2015). In vitro antioxidant and antitubercular activity of *Leucas marrubioides* desf. root extracts. *J. Appl. Pharm. Sci. 5*, 137–142.

Harley, R.M., Atkins, S., Budantsev, A.L., Cantino, P.D., Conn, B.J., Grayer, R., Harley, M.M., De Kok, R.D., Krestovskaja, T.D., Morales, R. and Paton, A.J. (2004). Labiatae. In *Flowering plants· Dicotyledons: Lamiales (except Acanthaceae including Avicenniaceae)* (pp. 167-275). Berlin, Heidelberg: Springer Berlin Heidelberg.

Hasan, M., Burdi, D. K., Ahmad, V. U. (1991). Leucasin, A Triterpene Saponin from *Leucas nutans*. *Phytochemistry*, 4181-4183

Hase, J., Bharati, G., Deshmukh, K., Phatangre, K., Rahane, N., & Dokhe Shital, A. (2016). Synthesis and characterization of Cu nanoparticles of L plant. *EJPMR*, *3*, 241-242.

Hashem, M. M., Salama, M. M., Mohammed, F. F., Tohamy, A. F., & El Deeb, K. S. (2019). Metabolic profile and hepatoprotective effect of *Aeschynomene elaphroxylon* (Guill. & Perr.). *PloS one*, *14*(1), e0210576.

Hossain, S., Rahman, M., Fatima, N., Haque, M., & Islam, J. (2013). *Leucas zeylanica* (L.) R. Br. protects ethanol and hydrogen peroxide-induced oxidative stress on hepatic tissue of rats. International Current Pharmaceutical Journal, 2(9), 148–151.

Hung, N.H., Thi Hong Chuong, N., Satyal, P., Hieu, H.V., Dai, D.N., Huong, L.T., Sinh, L.H., Thi Bich Ngoc, N., Hien, V.T. & Setzer, W.N. (2019). Mosquito larvicidal activities and chemical compositions of the essential oils of *Leucas zeylanica* growing wild in Vietnam. *Natural Product Communications*, *14*(6), 1934578X19842675.

Islam, A., Hussain, M.S., Sen, N., Abedin, F., Millat, M.S., Islam, M.S., Das, A., Kar, A. and Hossain, M.M. (2017). Investigation of in vitro thrombolytic and anti-helminthic activity and in vivo anxiolytic and antidepressant potentiality with phytochemical nature of methanolic extract of *Leucas lavandulifolia*. *Sustainable Chemistry and Pharmacy*, *6*, 61-66.

Islam, G., Gahlot, K., Mani, M., Kumar, P., & Shukla, D. (2020). Hepatoprotective activity of *Leucas cephalotes* against paracetamol induced hepatotoxicity in rats. *Research Journal of Pharmacy and Technology*, *13*(3), 1183-1186.

Jangra, P., Singh, J., & Singh, S. (2016). Antimicrobial activity of *Leucas Cephalotes* Spreng. *International Journal of Pharmaceutical Sciences and Research*, *7*(7), 2984.

Jayaweera, D. M. A. (1980). Medicinal plants (indigenous and exotic) used in Ceylon, Part IV. The National Science Council of Sri Lanka, Colombo, 1982:52–53.

Joshi, R. K. (2016). *Leucas aspera* (Willd.) Link Essential oil from India: β-caryophyllene and 1-octen-3-ol chemotypes. *Journal of Chromatographic Science*, *54*(3), 295–298.

Joshi, R. K. (2014). GC/MS analysis of the essential oil of *Leucas indica* from India. *Natural Product Communications*, *9*(11), 1934578X1400901119.

Kalpana, V. N., & Rajeswari, V. D. (2016). Phytochemical and pharmacological investigation of an indigenous medicinal plant *Leucas aspera*. *International Journal of PharmTech Research*, *9*(8), 2455-9563.

Kamble, S., & Rao, B. G. (2017). Effect of methanolic root extracts of ethnomedicinal plants on paracetamol induced hepatotoxicity in rats. *Journal of Pharmaceutical Research*, 63-67.

Katzung, G. B. (1992). *Basic and clinical pharmacology*. Appleton and Lange.

Kaur, R., & Kumar, N. (2016). Phytochemical composition and in vitro antioxidant activity of *Leucas aspera* leaves. *Research Journal of Pharmacy and Technology*, *9*(12), 2217-2221.

Khalil, A. T., Gedara, S. R., Lahloub, M. F., & Halim, A. F. (1996). Diterpenes and a Ffavone from *Leucas neufliseana*. *Phytochemistry*, 1569-1571.

Khandelwal, K. (2008). *Practical pharmacognosy*. Pragati Books Pvt. Ltd.

Khare, C. P. (2007). Encyclopedia of Indian Medicinal Plants. New York, Berling.

Kulkarni, R. R., Shurpali, K., Puranik, V. G., Sarkar, D., & Joshi, S. P. (2013). Antimycobacterial Labdane Diterpenes from *Leucas stelligera*. *Journal of Natural Products*, 1836-1841.

Kumar G. V, & Devanna N. (2016). An Update of *Leucas aspera* – A Medicinal Plant. *International Journal of Science Research Methodology*, 485-503.

Madhu, G. C., Jaianand, K., Rameshkumar, K., Balaji, P., & Veeramanikandan, V. (2019). In-vivo studies on anti-diabetic potential of *Leucas aspera* in streptozotocin induced diabetic wistar albino rats. *Journal of Drug Delivery and Therapeutics*, *9*(4-s), 105-110.

Manivannan, R. (2016). Isolation of apigenin-7-O-(6''-OE-caffeoyl)-β-D-glucopyranoside from *Leucas aspera* L. with anti-inflammatory and wound healing activities. *Journal of Pharmacy & Pharmacognosy Research*, *4*(2), 54-61.

Mannan, M. A. (2019). Evaluation of Antinociceptive Effects of Methanolic Extract of *Leucas aspera* Leaves in Mice. *EC Pharmacology and Toxicology*, *7*, 1001-1012.

Meghashri, S., Kumar, H. V., & Gopal, S. (2010). Anti-oxidant Properties of A Novel Flavonoid from Leaves of *Leucas aspera*. *Food Chemistry*, 105–110.

Minja, M. M. J. (1999). The Maasai wonder plants. In *Proceedings of the People and Plants Training Workshop held at the Tropical Pesticides Research Institute (TPRI)* (pp. 15-18).

Misra, T. N., Singh, R. S., Prasad, C., & Singh, S. (1992). Two aliphatic ketols from *Leucas aspera*. *Phytochemistry*, *32*(1), 199–201.

Moody, J. O., Gundidza, M., & Wyllie, G. (2006). Essential Oil Composition of *Leucas milanjiana* Guerke. *Journal of Fragrance and Flavour*, 872-874.

Mothana, R. A., Noman, O. M., Al-Sheddi, E. S., Khaled, J. M., Al-Said, M. S., & Al-Rehaily, A. J. (2017). Chemical composition, in vitro antimicrobial, free-radical-scavenging and antioxidant activities of the essential oil of *Leucas inflata* Benth. *Molecules*, *22*(3), 367.

Mothana, R. A., Al-Said, M. S., Al-Yahya, M. A., Al-Rehaily, A. J., & Khaled, J. M. (2013). GC and GC/MS analysis of essential

oil composition of the endemic Soqotraen *Leucas virgata* Balf. f. and its antimicrobial and antioxidant activities. *International Journal of Molecular Sciences*, *14*(11), 23129–23139.

Nagarajan, S. K., Rani, V., Narayanasamy, A., & Masthan, M. K. (2019). *Leucas aspera* to Treat Pan Oral Disorders-An Experimental Study. *Dental Journal*.

Napagoda, M., Gerstmeier, J., Butschek, H., Lorenz, S., Kanatiwela Niriella, D., de Soyza, S., & Werz, O. (2018). Lipophilic Extracts of *Leucas zeylanica*, A Multi-purpose Medicinal Plant in The Tropics, Inhibit Key Enzymes Involved in Inflammation and Gout. *Journal of Ethnopharmacology*, 474-481.

Nidhal, N., Zhou, X. M., Chen, G., Zhang, B., Han, C., & Song, X. (2020). Chemical constituents of *Leucas zeylanica* and their chemotaxonomic significance. *Biochemical systematics and ecology*, *89*, 104006.

Nipu, A. H., Akter, S., & Rahmatullah, M. (2017). Preliminary phytochemical screening and evaluation of antihyperglycemic and antinociceptive effects of a combination of *Leucas aspera* aerial parts and Zingiber officinale rhizomes. *World J Pharm Pharm Sci*, *6*(8), 135-145.

Pandey P., Mehta R., & Upadhyay R. (2013). Physico-chemical and Preliminary Phytochemical Screening of *Psoralea corylifolia*, *Archives of Applied Science Research*, 261-265.

Patel, N. K., Khan, M. S., & Bhutani, K. K. (2015). Investigations on *Leucas cephalotes* (Roth.) Spreng. for inhibition of LPS-induced pro-inflammatory mediators in murine macrophages and in rat model. *EXCLI journal*, *14*, 508.

Patil, K., Bagade, S., Sharma, S., & Hatware, K. (2019). Potential of herbal constituents as new natural leads against helminthiasis: A neglected tropical disease. *Asian Pacific Journal of Tropical Medicine, 12*(7), 291-299.

Pavunraj, M., Ramasubbu, G., & Baskar, K. (2017). *Leucas aspera* (Willd.) L.: Antibacterial, antifungal and mosquitocidal activities. *Trends in Phytochemical Research*, *1*(3), 135–142.

Pradhan, B. P., Chakraborty, D. K., Subba, G. C. (1990). A Triterpenoid Lactone from *Leucas aspera*. *Phytochemistry*, 1693-1695.

Prasad, R., Bisht, L. S., Joshi, D., Nailwal, M. K., & Melkani, A. B. (2017). Chemical Composition and Antibacterial Activity of the Essential Oil from Whole Aerial Parts of *Leucas mollissima* Wall. ex Benth. *Journal of Essential Oil Bearing Plants*, *20*(1), 141-147.

Priya, K. K., & Anuradha, V. (2019). A Novel Pyridyl Ester Isolated from *Leucas cephalotes*. *Asian Journal of Chemistry*, *31*(10), 2410–2412.

Radhika, B., Srilekha, Chaitanya, Sandhya, & Saikrishna. (2018). Pharmacognostic and Preliminary Phytochemical Evaluation of the Leaves of *Leucas zeylanica*. *International Journal of Biomedical Investigation*, 1-5.

Rahman, S. M., Mony, T., Ahammed, K., Naher, S., Haque, M. R., & Jui, S. M. (2018). Qualitative phytochemical screening and evaluation of analgesic and antidiarrheal activity of ethanolic extract of *Leucas cephalotes* leaves. *Journal of Pharmacognosy and Phytochemistry*, *7*(5), 1484-1492.

Rajesh, S. V., Gnanendra, T. S., & Kumar, T. S. (2021). Anti-inflammatory and molecular docking analysis of *Leucas vestita* wall. Ex. Benth. extract against cyclo-oxygenase-2. *Prostaglandins & Other Lipid Mediators*, *156*, 106581.

Ramalingam, R., Nath, A. R., Madhavi, B. B., & Nagulu, M. (2013). Invitro free radical scavenging, cytotoxic and acetylcholinesterase inhibitory activities of *Leucas martinicensis*. *International Journal of Chemical and Analytical Science*, *4*(2), 91-95.

Rupani, R., & Chavez, A. (2018). Medicinal plants with traditional use: Ethnobotany in the Indian subcontinent. *Clinics in Dermatology, 36*(3), 306-309.

Ryding O. (1998). Phylogeny of the Leucas Group (Lamiaceae). *Systematic Botany*, 23:235-47.

Sabri, G. U. L. N. A. A. Z., & Vimala, Y. (2018). Antibacterial and antioxidant activity of *Leucas aspera* flowers from Bihar, India. *Asian J Pharm Clin Res*, *11*(2), 223-226.

Sadhu, S. K., Okuyama, E., Fujimoto, H., & Ishibashi, M. (2006). Diterpenes from *Leucas aspera* Inhibiting Prostaglandin-Induced Contractions. *Journal of Natural Products*, 988-994.

Saito, K. (2018). Development of Plant Metabolomics and Medicinal Plant Genomics. *Yakugaku Zasshi-Journal Of The Pharmaceutical Society Of Japan, 138*(1), 1-18.

Satyal, P., Paudel, P., Poudel, A., & Setzer, W. N. (2012). Microbiological activities of volatile constituents of *Leucas aspera* (Willd.) Link from Nepal. *J. Nat. Pharm*, *3*(2), 118-119.

Scheen, A. C., & Albert, V. A. (2009). Molecular Phylogenetics of the Leucas Group (Lamioideae; Lamiaceae). *Systematic Botany*,173-181.

Shamsi-Baghbanan, H., Sharifian, A., Esmaeili, S., & Minaei, B. (2014). Hepatoprotective herbs, avicenna viewpoint. *Iranian Red Crescent Medical Journal*, *16*(1).

Sharma, R., Garg, N., Verma, D., Rathi, P., Sharma, V., Kuca, K., & Prajapati, P. K. (2021). Indian medicinal plants as drug leads in neurodegenerative disorders. In *Nutraceuticals in brain health and beyond* (pp. 31-45). Academic Press.

Shukla, P. K., Misra, A., Srivastava, S., & Rawat, A. K. (2016). Reversed phase high-performance liquid chromatographic ultra-violet (photo diode array) quantification of oleanolic acid and its isomer ursolic acid for phytochemical comparison and pharmacological evaluation of four Leucas species used in ayurveda. *Pharmacognosy Magazine*, *12*(Suppl 2), S159.

Spiegel, T. M. (1983). *Practical rheumatology*, Wiley, Medical Publication John Wiley and sons, USA, 161–163, 169-172 and 178-183.

Srivastava J, Lambert J, & Vietmeyer N. (1996). Medicinal Plants: An Expanding Role in Development. *World Bank Technical Paper*, 320.

Sunojkumar, P., & Mathew, P. (2008). South Indian Leucas: A Taxonomic Monograph. *Centre for Research in Indigenous Knowledge Science and Culture, Calicut*.

Tahareen, S., Shwetha, R., & Myrene, R. D. (2016). Potential antioxidant, anti inflammatory and antibacterial evaluation of extracts of *Leucas aspera* using in vitro models. *International Journal of Pharmacy and Pharmaceutical Science*, *8*(11), 292-297.

Ugwah-Oguejiofor, C. J., Eze, U. A., Bello, S. O., Etuk, U., Ameh, I. & Ugwah, M. (2015). Anticonvulsant and Sedative Activities of Aqueous Leaf Extract of *Leucas martinicensis* (Jacq.) R. Br. *Nigerian Journal of Basic and Applied Science*, 87-91.

Verma, A., Kumar, A., Upreti, D. K., Pande, V., & Pal, M. (2017). Fatty acid profiling and In vitro antihyperglycemic effect of *Leucas cephalotes* (Roth) spreng via carbohydrate hydrolyzing enzyme inhibition. *Pharmacognosy Magazine*, *13*(Suppl 1), S22.

Wu, P. S., Jeng, J., Yang, J. J., Kao, V., Yen, J. H., & Wu, M. J. (2020). *Vernonia patula* (Dryand.) Merr. and (Retz.) R. Brown exert anti-inflammatory activities and relieve oxidative stress via Nrf2 activation. *Journal of Ethnopharmacology*, *262*, 113155.

Zahra, W., Rai, S.N., Birla, H., Singh, S.S., Rathore, A.S., Dilnashin, H., Keswani, C. and Singh, S.P. (2020). Economic importance of medicinal plants in Asian countries. *Bioeconomy for sustainable development*, 359-377.

Zhang, X., Gui, M., Zhang, C., Chen, C., Yu, L., & Liu, J. (2016). Leucasinoside: A new abietane diterpenoid glycoside from *Leucas zeylanica*. *Records of Natural Products*, *10*(5), 645.

Zielinska S, Matkowski A. (2014). Phytochemistry and Bioactivity of Aromatic and Medicinal Plants from The Genus Agastache (Lamiaceae). *Phytochemistry Reviews*, 391–416.