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LIMNOPHILA (SCROPHULARIACEAE): CHEMICAL AND PHARMACOLOGICAL ASPECTS

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ABSTRACT

The present resume covers an up-to-date and detailed literature on *Limnophila* species (family: Scrophulariaceae) and the botanical classification, ethno-pharmacology, chemical constituents as well as the biological activities and pharmacological applications of both isolated phytochemicals and plant extracts. There are about forty plant species belonging to this genus. Various classes of chemical constituents like flavonoids, terpenoids, amino acids etc. have been reported from the genus. Crude plant extracts and the isolated chemical constituents exhibited different biological activities such as antimicrobial, anti-inflammatory, anti-oxidant, cytotoxic, wound healing, hypotensive activity etc. The review covers literature upto September, 2014 enlisting 131 chemical constituents and citing 88 references.

KEYWORDS: Biological activity, Chemical constituents, Ethno-pharmacology, *Limnophila* Genus, Taxonomical classification.

INTRODUCTION

Limnophila[1-5] is commonly known as '*Ambulia*' and exists in aquatic environments. "It is tropical to subtropical in Australia, Africa as well as Pacific Islands, a perennial from Southeast Asia and has adventives distribution in North America.[3] Plants belonging to *Limnophila* genus are reported to be widely distributed in India, and cover an important position in traditional systems of medicine—where a number of species are being used as folk medicines in the treatment of various ailments; crude plant extracts as well as isolated phytochemicals exhibited various significant biological activities. Therefore, a total

compilation regarding chemical and pharmacological aspects of this important genus is urgent and hence motivated the authors to undertake this review work. Although few works[6-10] on chemical and pharmacological aspects of different species of *Limnophila* have already been reported but this review presents an up to date compilation on *Limnophila* genus as a whole which will be much helpful to the present day researchers working in this direction. A look into the amount of work done so far on this genus, it shows that a significant portion remains unexplored. Therefore, this review is being presented to stimulate the researchers working in this field to carry out further research work on this important genus so as to explore this important genus for the betterment of mankind. The present review work includes the update reported ethnobotany, biological, pharmacological and phytochemical studies of the genus *Limnophila* as well as phytochemicals as reported so far from this genus.

BOTANICAL ASPECTS

Limnophila[11,12] is an aquatic and perennial herb; its natural habitats are ponds, rivers, lakes as well as marshy lands. Stems are generally not more than 12 feet length, whereas the emergent stems remains usually 2 to 15 cm above the surface of water. The flowers are stalk less and borne in the leaf axis, and are axillary and solitary or in axillary or terminal spikes or racemes, sessile or pedicellate. The lower portion has five, green and hairy lobes having length of 4-5 mm. The upper portion is purple in colour and contains five fused petals making a tube with two lips. The fruit is capsule having capacity to contain up to 150 seeds. *Limnophila* is reproduced through fragmentation of the stem and seeds fruits are matured in post-rainy session. As per the literature survey, out of the 40 species of *Limnophila* genus, few species like *L. indica, L. rugosa, L. heterophylla, L. aromatica, L. conferta, L. geoffrayi* are assessed for their chemical and pharmacological studies (**Table 1**); other species are either less abundant in nature or not yet been undertaken for chemical and pharmacological investigation.

Table 1. List of *Limnophila* species

Species of *Limnophila*	
L. aromatica (Lamarck) Merrill. (Syn. *L. aromaticoides* Yang & Yen *L. gratissima* Blum)	*L. indica* (Linnaeus) Druce (Syn. *L. Gratioloides* R. Brown, *L. Racemosa* Bentham, *L. aquatica* Roxburgh)
L. australis Wannan & Waterh.	*L. laotica* Bonati
L. balsamea (Benth.) Benth. (Syn. *L thorelii*Bonati).	*L. laxa* Bentham
L. borealis Y. Z. Zhao & Maf.	*L. micrantha* (Benth.) Bentham

L. brownii Wannan	*L.parviflora* Yamazaki
L. chinensis (Osbeck) Merill (Syn. *L. chevalieri* Bonati, *L. hi*rsuta (Heyne ex Benth.) Benth.	*L. poilanei* Yamazaki
L. connata (Buchanan-Hamilton ex D. Don) Handel-Mazzetti	*L. polyantha* Kurz ex Hook.f. (Syn. *L. polyantha* Yamazaki)
L. dasyantha Skan	*L. repens* (Bentham) Bentham Syn. *L. conferta* Bentham (*L. dubia* Bonati *L. sessilis* (Bentham) Fischer
L. erecta Bentham	*L. rugosa* (Roth) Merill (Syn. *L. roxburghii* G. Don)
L. fragrans Seem	*L. sessiliflora* (Vahl) Blume
L. glabra (Benj.) Kerr	*L. siamensis* Yamazaki
L. geoffrayi Bonati	*L. taoyuanensis* Yang & Yen
L. gigantean	*L. ceratophylloides*
L. hayatae Yamazaki	*L. verticillata* Yamazaki
L. heterophylla (Linnaeus) Druce (Syn. *L. reflexa* Bentham)	*L. villifera* Miq.
L. hottonoides Druce	*L. X ludoviciana* Thieret
L. tenera	

TAXONOMY OF *LIMNOPHILA* PLANTS

The taxonomical classification[13,14] of *Limnophila* plants are shown below (**Table 2**):

Table 2: Taxonomical Classification

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Scrophulariales
Family	Scrophulariaceae
Genus	*Limnophila* R. Brown

About 40 species[15] of the genus *Limnophila* are known; traditional uses of some important species are cited here:

TRADITIONAL USES

Limnophila plants are extensively used as herbal medicine, and are found to be useful and effective in the treatment of various ailments as mentioned below on the basis of exhaustive literature survey.

(i) *L. aromatica (Syn. L. gratissima)*: The plant is used as spinach and eaten both as raw or steamed. The plant is used as anthelmintic, anti-inflammatory, antiseptic, aperients, appetizer,

carminative, digestive, diuretic, febrifuge and galactagogue. It is found to be effective in vitiated conditions of *pitta*, foul ulcers, agalactia, galactic impurities, anorexia, dyspepsia, helminthiasis, constipation, inflammations and strangury. The juice of the plant is applied as a cooling medicine in fever and pharyngitis. It is given to nursing women, when the milk is sour.[7] The plant emits turpentine-like odour and yields an essential oil of 0.13%.[3, 6-7, 16-20] In Southeast Asia, this plant is reported to use as a medicinal plant and spice.[21-22]

(ii) *L. rugosa (Syn. L. roxburghii)*: The plant shows various applications in the traditional medicine system. The juice of the plant is rubbed over the body in pestilent fever and is applied with coconut oil for the treatment of elephantiasis. It is used in diarrhoea, dysentery and dyspepsia, and also used as carminative and tonic. The essential oil of this plant also exhibits significant anti-bacterial and anti-fungal activities and is applied as flavouring agent of food and perfuming of hair oils. The plant had been accepted for "*Sugandhabala*" as it responded to Ayurvedic description of the drug.[8] Infusion of leaves is reported to use as diuretic as well as stomachic in the Philippine Islands and more or less in India.[6, 8, 16-20] In Odisha, the traditional practitioners use *L. rugosa* as a source plant of *Bhringaraja*.[23] The plant is also reported to exhibit wound healing activity.[24]

(iii) *L. indica (Syn. L. gratioloides, L. racemosa, L. aquatica)*: The plant has a refreshing and agreeable odour resembling to camphor or oil of lemon. *L. indica* is considered to be carminative and antiseptic. A liniment prepared from the plant is used for the treatment of elephantiasis and the juice of the plant is used in pestilent fevers. It is given internally in dysentery combined with ginger, cumin and other aromatics.[6, 9,16-20]

(iv) *L. conferta:* The plant has been employed to treat various types of skin diseases and conditions of inflammation in the indigenous system of medicine.[6, 25-26]

(v) *L. geoffrayi:* *L. geoffrayi* Bonati is used as an antidote for poison detoxification and is considered as a vegetable in north-eastern Thailand.[27] This species is also used as a traditional medicine due to its antipyretic, expectorant, and galactogogue properties.[27]

(vi) *L. heterophylla:* *L. heterophylla* is locally known as 'Ambakasia' by tribal people of Odisha and finds lot of applications in the traditional system of medicine against various ailments.[10, 19, 28-30] Ethnic people from hill ranges generally use this plant in hair oil

preparation.[23] The plant leaves are crushed with coconut oil and applied on the wound to quicken healing.[31]

RESULTS AND DISCUSSION

CHEMICAL CONSTITUENTS FROM LIMNOPHILA

The phytochemical research of the genus *Limnophila* afforded so far a total of **131** compounds having varying structural skeletons. These compounds are classified into flavonoids (**1-26**; **Fig. 1**) [**Table 3**], terpenoids (**27-87**; **Fig. 2**) [**Table 4**], amino acids (**88-105**; **Fig. 3**) [**Table 5**] and miscellaneous (**106-131**; **Fig. 4**) [**Table 6**]. These are presented below:

Table 3: **Flavonoid Constituents of *Limnophila***

Compounds (Str. No.)	Source	Ref.
5,7-Dihydroxy-3,6,3',4'-tetramethoxyflavone (7-desmethyl artemetin, **1**)	*L. gratissima* (aerial parts and roots)	32
5,7-Dihydroxy-6,8,4'-trimethoxyflavone (Nevadensin, **2**)	*L. geoffrayi* (aerial parts) *L. heterophylla* (aerial parts and roots) *L. rugosa* *L. gratissima* (Whole plant) *L. aromatica*(aerial parts)	27, 33 34 35 36 37
5-Hydroxy-6,7,8,4'-tetramethoxyflavone (Gardenin B, **3**)	*L. geoffrayi* (aerial parts) *L. aromatica*(aerial parts)	33 37
Nevadensin-7-*O*-β-D-glucopyranoside (**4**)	*L. aromatica* (aerial parts)	37
5,8,4'-Trihydroxy-6,7-dimethoxyflavone (Isothymusin, **5**)	*L. geoffrayi* (aerial parts) *L. aromatica* (aerial parts)	27, 33 37
Pilosin (**6**)	*L. aromatica* (aerial parts)	37
8-Hydroxysalvigenin (**7**)	*L. aromatica*(aerial parts)	37
5-Hydroxy-6,7,4'-trimethoxyflavone (Salvigenin, **8**)	*L. rugosa* (aerial parts and roots) *L. gratissima* (Whole plant), *L. aromatica* (aerial parts)	38 36 39

Compounds (Str. No.)	Source	Ref.
Pectolinaringenin (**9**)	*L. aromatica* (aerial parts)	37
5,8-Dihydroxy-6,7,4'-trimethoxyflavone (**10**)	*L. indica* (aerial parts and roots)	40
5,7-Dihydroxy-6,8,3',4'-tetramethoxyflavone (Hymenoxin, **11**)	*L. heterophylla*	26
5,7,4'-Trihydroxy-6,8-dimethoxyflavone (Demethoxysudachitin, **12**)	*L. rugosa*	35
5-Hydroxy-7,2',4'-trimethoxyflavone (**13**)	*L. rugosa* (aerial parts and roots)	41
5-Hydroxy-7,8,2',4'-tetramethoxyflavone (**14**)	*L. rugosa* (aerial parts and roots) *L. heterophylla* (aerial parts and roots)	42 43
5,7-Dihydroxy-8,3',5'-trimethoxyflavone (**15**)	*L. rugosa* (aerial parts and roots)	44
5,2'-Dihydroxy-7,8,4'-trimethoxyflavone (**16**)	*L. heterophylla* (aerial parts and roots)	45
5,2',4'-Trihydroxy-7-methoxyflavone (Artocarpetin, **17**)	*L. rugosa* (aerial parts and roots)	46
7-*O*-Methylwogonin (**18**)	*L. indica* (whole plant)	47-48
Skullcapflavone I (**19**)	*L. indica* (whole plant)	47
5-Hydroxy-7,2'-dimethoxyflavone (**20**)	*L. indica* (whole plant)	47-48
5-Hydroxy-6,8-dimethoxy-3',4'-methylene-dioxyflavone (**21**)	*L. indica* (aerial parts and roots)	49
5,2'-Dihydroxy-8,3',4'-trimethoxyflavone (**22**)	*L. indica* (aerial parts and roots)	48, 50
3',4'-Ethylenedioxy-5-hydroxy-3-(1-hydroxy-1-methylethyl)-6,7-dimethyl-5'-methoxyflavone-8-carboxylic acid (**23**)	*L. indica* (aerial parts and roots)	51
5,7,2',5'-Tetramethoxyflavone (**24**)	*L. indica* (aerial parts and roots)	47
5,7,3',4'-Tetramethoxyflavanone (**25**)	*L. indica* (aerial parts and roots)	47
5,6-Dihydroxy-7,8,4'-trimethoxyflavone (**26**)	*L. indica* (aerial parts and roots)	47-48

Table 4: **Terpenoid Constituents of *Limnophila***

Compounds (Str. No.)	**Source**	**Ref.**
1 β -Hydroxy-3-keto-olean-12-en-28-oic acid (**27**)	*L. rugosa* (aerial parts and roots)	52
Methyl-olean-12-ene-3 α -benzoyloxy-29-carboxylate (**28**)	*L. heterophylla* (aerial parts and roots)	53
3 α -Hydroxyolean-12-ene-29-oic acid (Katonic acid, **29**)	*L. heterophylla* (aerial parts and roots)	54
Ursolic acid (**30**)	*L. heterophylla* (aerial parts and roots) *L. rugosa* (aerial parts and roots)	43 55
Betulin (**31**)	*L. rugosa*	56
Betulinic acid (**32**)	*L. rugosa* *L. geoffrayi* (aerial parts)	56 33
4-*Epi*-hederagenin (**33**)	*L. geoffrayi* (aerial parts)	33
6*β*-Hydroxyoleanolic acid (**34**)	*L. geoffrayi* (aerial parts)	33
Rotungenic acid (**35**)	*L. geoffrayi* (aerial parts)	33
Uncaric acid (**36**)	*L. geoffrayi* (aerial parts)	33
3 β -Hydroxy-lup-20(29)-en-27-oic acid (**37**)	*L. rugosa*	35
3-Oxo-olean-12(13),18(19)-dien-29α-carboxylic acid (**38**)	*L. indica* (Aerial parts and roots)	57
(+)-Limonene (**39**)	Essential oil of *L. heterophylla* Essential oil of *L. aromatica* Essential oil of *L. geoffrayi*	59 58 60
Linalool (**40**)	Essential oil of *L. rugosa* Essential oil of *L. aromatica*	59
Humulene (**41**)	Essential oil of *L. rugosa*	59
Caryophyllene (**42**)	Essential oil of *L. rugosa* Essential oil of *L. aromatica*	59 58
(+)-Cadinene (**43**)	Essential oil of *L. heterophylla* Essential oil of *L. erecta*	59 61
α -Pinene (**44**)	Essential oil of *L. heterophylla* Essential oil of *L. aromatica* Essential oil of *L. erecta*	59 58 61
β-Pinene (**45**)	Essential oil of *L.*	62

Compounds (Str. No.)	Source	Ref.
	aromatica	
p-Cymene (**46**)	Essential oil of *L. heterophylla*	59
Thymol (**47**)	Essential oil of *L. conferta*	26
α -Phellandrene (**48**)	Essential oil of *L. conferta*	26
β -Phellandrene (**49**)	Essential oil of *L. conferta*	26
β -Ocimene (**50**)	Essential oil of *L.conferta*	26
Trans- β -farnesene (**51**)	Essential oil of *L.conferta* Essential oil of *L. aromatica*	26
β -Selinene (**52**)	Essential oil of *L.conferta*	26
Terpinen-4-ol (**53**)	Essential oil of *L.conferta*	26
Borneol (**54**)	Essential oil of *L.conferta*	26
Nerol (**55**)	Essential oil of *L.conferta*	26
Dihydroumbellulone (**56**)	Essential oil of *L.conferta*	26
α -Eudesmol (**57**)	Essential oil of *L. heterophylla*	59
α -Bulnesene (**58**)	Essential oil of *L. rugosa*	59
Camphene (**59**)	Essential oil of *L. aromatica*	63
Sabinene (**60**)	Essential oil of *L. aromatica*	63
β-Myrcene (**61**)	Essential oil of *L. aromatica*	63
2-Carene (**62**)	Essential oil of *L. aromatica*	63
Z-Ocimene (**63**)	Essential oil of *L. aromatica*	63
E-Ocimene (**64**)	Essential oil of *L. aromatica*	63
γ-Terpinene (**65**)	Essential oil of *L. aromatica*	63
Terpinolene (**66**)	Essential oil of *L. aromatica*	63
(-)-Camphor (**67**)	Essential oil of *L. aromatica*	63
Cis-Limonene oxide (**68**)	Essential oil of *L. aromatica*	62
Trans-Limonene oxide (**69**)	Essential oil of *L. aromatica*	62
Bornyl acetate (**70**)	Essential oil of *L. aromatica*	62
Perillaldehyde (**71**)	Essential oil of *L. aromatica* Essential oil of *L. geoffrayi*	62,64 60
Borneol (**72**)	Essential oil of *L. aromatica*	62

Compounds (Str. No.)	Source	Ref.
Trans- Shisool (**73**)	Essential oil of *L. aromatica*	62
α-Terpineol (**74**)	Essential oil of *L. aromatica*	62
D-Limonene (**75**)	*L. indica*. (Essential oil) Essential oil of *L. erecta*	65 61
D-Perillaldehyde (**76**)	*L. indica*. (Essential oil)	65
d-Pulegone (**77**)	Essential oil of *L. geoffrayi*	60
α-Humulene(**78**)	Essential oil of *L. aromatica*	62-63
L-Caryophyllene (**79**)	Essential oil of *L. aromatic* Essential oil of *L. erecta*	63 61
Caryophylleneoxide (**80**)	Essential oil of *L. aromatica*	63
p-Cymen-8-ol (**81**)	Essential oil of *L. aromatica*	63
Cis-4-caranone (**82**)	Essential oil of *L. aromatica*	64
Trans-4-caranone (**83**)	Essential oil of *L. aromatica*	64
Caranyl acetate (**84**)	Essential oil of *L. aromatica*	62
2,6,10-Cycloundecatriene-1-one, 2,6,9,9-tetramethyl (**85**)	Essential oil of *L. aromatica*	63
12-Oxabicyclo[9.1.0]dodeca-3,7-diene,1,5,5,8-tetramethyl (**86**)	Essential oil of *L. aromatica*	63
1,3-Cyclohexadiene-1-methanol,4-(1-methylethyl) (**87**)	Essential oil of *L. aromatica*	63

Table 5: Amino Acid Constituents of *Limnophila*

Compounds (Str. No.)	Source (Plant Parts)	Ref.
Aspartic acid (**88**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Threonine (**89**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Serine (**90**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Glutamic acid (**91**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Proline (**92**)	*L. rugosa*. (Whole plant)	60
Glycine (**93**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Alanine (**94**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Valine (**95**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65

Compounds (Str. No.)	Source (Plant Parts)	Ref.
Isoleucine (**96**)	*L. rugosa*. (Whole plant)	60
Leucine (**97**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Tyrosine (**98**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Phenylalanine (**99**)	*L. rugosa*. (Whole plant)	60
Ornithine (**100**)	*L. rugosa*. (Whole plant)	60
Lysine (**101**)	*L. rugosa*. (Whole plant)	60
Histidine (**102**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
Arginine (**103**)	*L. rugosa*. (Whole plant) *L. indica*. (Leaves)	60 65
γ-Aminobutyric acid (**104**)	*L. rugosa*. (Whole plant)	60
Cystine (**105**)	*L. indica*. (Leaves)	65

Table 6: Miscellaneous Constituents of *Limnophila*

Compounds (Str. No.)	Source	Ref.
p-Methoxybenzoic acid (**106**)	Essential oil of *L. rugosa*	66
Anisaldehyde (**107**)	Essential oil of *L. rugosa*	66
Anisylacetone (**108**)	Essential oil of *L. rugosa*	60
Trans-anethole (**109**)	Essential oil of *L. rugosa*	60
Cis-anethole (**110**)	Essential oil of *L. rugosa*	60
Methylchavicol (**111**)	Essential oil of *L. rugosa*	66
Formic acid (**112**)	Essential oil of *L. rugosa*	66
Propionic acid (**113**)	Essential oil of *L. rugosa*	66
Acetic acid (**114**)	Essential oil of *L. rugosa*	66
Valeric acid (**115**)	Essential oil of *L. rugosa*	66
Acetone (**116**)	Essential oil of *L. rugosa*	66
Hentriacontanol (**117**)	Essential oil of *L. rugosa*	56
Limnophila-spiroketone (**118**)	*L. geoffrayi* (aerial parts)	33
3-Farnesyl-4-hydroxybenzoic acid (**119**)	*L. geoffrayi* (aerial parts)	33
Benzene (**120**)	Essential oil of *L. aromatica*	64
2,4-Pentanedione (**121**)	Essential oil of *L. aromatica*	64
l-Octen-3-ol (**122**)	Essential oil of *L. aromatica*	64
Demethoxy-ageratochromene (**123**)	Essential oil of *L. aromatica*	64
Triethylcarbinol (**124**)	Essential oil of *L. aromatica*	64
Eugenol (**125**)	Essential oil of *L. aromatica*	67
3-Hexen-2-one(**126**)	Essential oil of *L. aromatica*	64
5-Nonenol-5-methyl (**127**)	Essential oil of *L. aromatica*	64
Acetic acid, tricyclo [4.4.0.0(3,8)] dec-9-en-4-yl ester (**128**)	Essential oil of *L. aromatica*	64
Caffeic acid (**129**)	*L. gratissima* (Whole plant), Essential oil of *L. aromatica*	37, 39
Cholrogenic acid (**130**)	*L. gratissima* (Whole plant), Essential oil of *L. aromatica*	37, 39
β-Sitosterol (**131**)	*L. indica*. (Aerial parts and roots)	49

BIOLOGICAL/PHARMACOLOGICAL ACTIVITIES OF CRUDE PLANT EXTRACTS AND THE ISOLATED CHEMICAL CONSTITUENTS

Various biological/pharmacological studies on different parts of *Limnophila* plants as crude extracts and also of pure chemical constituents isolated from these plant species have been carried out so far. Each biological/pharmacological activity has been discussed in detail below.

Antimicrobial activity

Limnophila plants have been found to exhibit notable antimicrobial activity.[6] *L. racemosa* and *L. indica* extracts were found to inhibit *in vitro* the growth of *Xanthomonas campestris* and *X. Malvacearum.*[68] Mishra *et al.*[69] also reported the antimicrobial activity of the same plant extracts against a number of bacterial species and obtained promising result (**Table 7.1**) on the basis of which they pointed out that both the extracts of *L. racemosa* and *L. indica* bears certain antimicrobial components.

Table 7.1: Antimicrobial activity of *L. racemosa* and *L. indica*

Species	*L. racemosa* (whole plant)	*L. indica* (whole plant)	Control
Bacillus anthracis	29	18	28
Bacillus mycoides	30	28	24
Bacillus pumilus	28	25	20
Bacillus subtilis	32	30	20
Pseudomonas sp.	25	26	26
Salmonella paratyphii	24	25	22
Staphylococcus albus	22	26	18
Xanthomonas campestris	19	18	16
Xanthomonasmalvacearum	20	17	16
Values refers Diameter of the Inhibition Zone Including Diameter of Well (10 mm) in mm			

The pentacyclic triterpenoid (**38**) isolated from *L. indica* was found to exhibit significant antibacterial activity against some *Gram*-positive bacteria -- *Bacillus subtilis*, *Staphylococcus aureus* and *Listeria monocytogenes* having MIC values in the range of 25–30 μg/mL and moderate activity against four *Gram*-negative bacteria such as *Salmonella typhimurium*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Pantoea ananatis* with MIC values within 30–100 μg/mL range[57] However, the compound (**38**) showed less potency against plant pathogenic bacterium *P. ananatis* and human pathogenic bacterium *S. typhimurium* (MIC values of 75 and 100 μg/mL, respectively). The investigators also reported that this compound (**38**) inhibited the growth of *B. subtilis* and *P. aeruginosa* completely with

bactericidal mode of action at their MIC values.[57] The compound on treatment with both the bacteria (*B. subtilis* and *P. aeruginosa*) affected the change of morphology towards pleomorphicity and released appreciable amount of nucleic acid in the external medium.[57]

The flavone, 5,6-dihydroxy-7,8,4'-trimethoxyflavone (**26**), isolated from the same plant is found to exhibit moderate antimicrobial efficacy against two Gram-negative bacteria such as *E. coli*, *S. typhimurium*, two Gram-positive bacteria such as *B. subtilis*, *S. aureus*, and two fungal pathogens such as *Alternaria solani* and *Candida albicans*.[70] The compound killed effectively *B. subtilis* by cell lysis mechanism. This flavonoid compound **26** was found to decrease the activity of phosphofructokinase and isocitrate dehydrogenase but enhance the activity of gluconeogenic fructose bisphosphatase at some sub-lethal dose.[70]

Sandhya *et al.*[71-72] concluded that *L. Indica* may be suitable and better substitute for the various synthetic anti-dysentery and antidiarrheal agents available in the market as they observed competent antibacterial as well as antidiarrheal efficacy of the plant with mild antacid activity as well. The investigators found the presence of phenolic compounds, flavonoids, alkaloids, fats and oils in the methanolic extract of *L. Indica* and reported that this extract is found to exhibit significant antibacterial potential against some bacterial strains such as *B. subtilis*, *S. aureus*, *P. aerugenosa* and *E. coli* as well as three antibiotic-resistant *Shigella* species (*S. flexneri*, *S. dysentery* and *S. boydii*) having MIC value in the range of 180 to 335 µg/mL (**Table 7.2**). The methanol extract also exhibited *in vivo* antidiarrheal activity in a dose dependent manner against castor-oil induced diarrhoea on Wistar albino rats the lowest dose at 100 mg/Kg showed better efficacy than loperamide used as standard control.[71] Furthermore, the extract exhibited moderate *in vitro* antacid activity on artificial stomach model.[71]

Table 7.2: MIC value for the antimicrobial activity of the methanolic extract of *L. indica*

Microorganism used	MIC value (µg/mL)
Bacillus subtilis	335
Staphylococcus aureus	180
Pseudomonas aerugenosa	190
Escherichia coli	225
Shiegella flexneri	230
Shigella dysentery	233
Shigella boydii	235

Chloroform extract of the aerial parts of *L. geoffrayi* also found to possess antimycobacterial activities.[27]

The essential oil of *L. geoffrayi* possessed high antimicrobial activity (measured by agar- and broth-dilution methods) against microorganisms generally present in contaminated cosmetic products having minimum inhibitory concentrations (MIC) values ranging from 0.03 to 0.2% per unit volume. Again, at a dose of 5µl/disc strong insecticidal activity of the oil as a fumigant with a 94% mortality was observed. Perillaldehyde (**71**), one of the constituents of this essential oil, found to be the most active in this regard.[60]

Antibacterial efficacy of the essential oil of *L. conferta* was also reported by Reddy *et al*.[26] against two Gram-positive bacteria such as *S. aureus* and *B. subtilis*, and two Gram-negative bacteria, *E. coli* and *P. aeruginosa***.** The significant antimicrobial activity of the essential oil of *L. conferta*, comparable with that of chloramphenicol used as standard and ethylene glycol as control solvent justifies the use of this plant in the indigenous system of medicine in controlling some infections. Moreover, the oil was not found to be toxic at a dose level of 1.6 mL/Kg orally. The essential oil of *L. conferta* is also a useful antifungal antidote. The antifungal activity of the oil at 1: 50 dilution in ethylene glycol was found to be of the same order as that of griseofulvin in chloroform used as standard (100 µg/0.1ml). The oil at a concentration of 100 µg/mL inhibited the growth of two fungi *viz. Trichophyton mentagrophytes* and *Microsporum gypseum.*[26]

A promising antifungal efficacy of *L. gratissima* (essential oil) was reported by Venkata Rao *et al*.[64] At a dose of 0.1 mL, the essential oil of the plant showed inhibition zones of 20, 28 & 25 mm (diameter) respectively against *Aspergilus niger*, *Rhizopus oryzae* and *Candida albicans* while the reference standard, griseofulvin exhibited the respective inhibition zones of 18, 24 & 14 mm at a dose of 100 mg in $CHCl_3$. It appeared that the oil of *L. gratissima* is mostly active against *Rhizopus oryzae*, and the efficacy is greater than grisofulvin thus the above findings are in support with the traditional uses of the plant oil as antiseptic.[64] Rao *et al.* [64] also reported that the essential oil of *L. gratissima* shows significant antimicrobial activity (**Table 7.3**) of the same order of that of the reference standards, streptomycin and chloramphenicol.

Table 7.3: Antimicrobial activity of *L. gratissima*

Bacteria	Diameter of inhibition zone (mm)		
	Essential oil *L. gratissima* (0.1mL)	Chloramphenicol (positive control) 25µg	Streptomycin (positive control) 50µg
Bacillus subtilis	18	19	21
Staphylococcus aureus	16	15	21
Escherichia coli	14	18	23
Pseudomonas aeruginosa	15	17	20

Further, Kapil *et al*.[29] reported that essential oil of *L. rugosa* as well as its phytochemicals exhibit significant anti-bacterial potential against two bacteria such as *B. subtilis* and *S. typhi.* The essential oil is also found to exhibit antifungal activity.[20] Both aqueous and alcoholic leaf extract of the plant was found to show antimicrobial efficacy (measured by Disc diffusion method) against some Gram-positive and Gram-negative bacteria such as *E. coli*, *S. aureus*, *B. subtilis*, *P. aeruginosa*, *S. typhi* and *Vibrio cholera.*[73] Another research group[74] reported significant antimicrobial efficacy of the methanol extract of leaf (as measured by Agar disc diffusion method) against medically important human pathogenic bacteria like *S. aureus*, *S. pyogenes*, *E. coli* and *P. aeruginosa* as well as three fungal strains such as *A. niger*, *A. clavatus* and *C. albicans*. Nanasombat and Teckchuen[75] reported antibacterial efficacy (measured by disc diffusion method) of methanol extract of *L. aromatica* leaves against a number of bacteria (**Table 7.4**) and noted promising antibacterial activity (MIC value ranging from 2.6 to 41.7 mg/mL). The extract was found to be more potent against two pathogens like *B. cereus* and *S. aureus* out of the tested bacteria.[75]

Table 7.4: Antibacterial activity of crude methanol extract of *L. aromatica* leaves

Microorganisms	Diameter of inhibition zone (mm)	MIC value (mg/mL)
Bacillus cereus	21.0 ± 5.2	2.6
Listeria monocytogenes	12.2 ± 3.4	20.8
Pseudomonas fluorescens	9.7 ± 4.2	20.8
Salmonella typhimurium	8.7 ± 0.6	10.4
Staphylococcus aureus	12.5 ± 2.5	2.6
Yersinia enterocolitica	11.2 ± 3.9	41.7

The disease, melioidosis, generally occurs in South-East Asia and Northern Australia and is caused by *Burkholderia pseudomallei*. Crude methanol extract of the *L. aromatica* was found to exhibit weak antimicrobial activity against this agent. The extract at a concentration of 2.5 mg/disc (measured by disc diffusion method) exhibited inhibition zone 8 mm each and also MIC and MBC values greater than 128 mg/mL against two strains of *B. pseudomallei* (A2

and G207) showing.[76] Ethanol extract of *L. aromatica* was also found to exhibit antibacterial potentials against *S. aureus, S. epidermidis, S. pyrogens* and *Propionibacterium acnes.*[77]

Nevadensin (**2**), a flavone isolated from several *Limnophila species*, was also reported to exhibit antimicrobial activities against a number of microbial strains including bacteria and fungi such as *B. subtilis, S. aureus, E. coli, S. typhimurium, A. solani*, and *C. albicans.*[70] The compound **2** showed bactericidal effect against *E. coli* (Gram-positive bacteria) and *S. aureus* (Gram-negative bacteria) having MIC values of 200 and 250 µg/mL, respectively and also found to inhibit the growth of *A. solani* (a fungal strain).[70] A research group[78] reported significant antibacterial as well as anti-fungal activities of the ethanol extract of the whole plant of *L. heterophylla*. The extracts at concentrations of 5, 25, 50 100 and 250 µg/mL exhibited remarkable inhibition activity against two pathogenic Gram-positive bacterial strains (*B. subtilis* and *S. aureus*), two pathogenic Gram-negative bacterial strains (*E. coli* and *K. pneumoniae*) as well as two fungal strains such as *S. flavus* and *C. albicans.*[78]

Anti-inflammatory activity

Reddy *et al*.[26] studied the anti-inflammatory activity of the essential oil and crude extract of *L. conferta* and also of nevadensin (**2**, a chemical constituent isolated from the plant), in acute and chronic inflammatory model following the method of Winter *et al*.[79] In tests for acute inflammatory activity, nevadensin (**2**) showed significant inhibition (P< 0.001, dose 75 mg/Kg oral, % inhibition 45.28) whereas the volatile oil and the crude extract unable to exhibit any significant activity compared to the control. However, in chronic inflammation model, the crude extract of the plant was found to reduce (P< 0.001, dose 500 mg/Kg/day oral) the weight of dry granuloma (22.1±1.4 mg % of body weight) compared to the control value (36± 1.86 mg % of body weight).The flavone, Nevadensin (**2**), isolated from the aerial parts and roots of the plant, was found to exhibit *in vitro* cyclooxygenase-1 and 2 (COX-1 and COX-2) inhibitory efficacy measured by COX catalyzed prostaglandin biosynthesis assay method [80]. The compound **2** was found to exhibit weak activity against the COX-2 (0.65% inhibition) but moderate inhibitory activity (7.37% inhibition) against COX-1 at 10µM concentration in DMSO. The investigators are in opinion that this compound may be used as a '*lead molecule*' for drugs against inflammatory and related diseases.[80]

Antitubercular activity

Nevadensin (**2**) and isothymusin (**5**), isolated from the chloroform extract of the aerial parts of *L. geoffrayi*, were reported to exhibit growth-inhibitory potential against *mycobacterium tuberculosis* H 37Ra having equal MIC value (200 µg/mL),[27] however the efficacy is relatively lower than those of the standard drugs (used during the experiment) rifampicin (MIC 0.003-0.0047 µg/mL), isoniazid (MIC 0.025-0.05 µg/mL) and kanamycin sulphate (MIC 1.25-2.5 µg/mL). But the flavone, nevadensin **(2)** was found to be more effective (MIC values: 100 µg/mL for nevadensin 10µg/mL for streptomycin used as standard) against the H 37Rv strain of *M. tuberculosis* as reported by Reddy *et al.*[26] The investigators suggested that the compound shows no toxicity up to 600 µg/Kg orally in acute toxicity studies.

Wound healing activity

The crude alcoholic extract of *L. conferta* was reported to have wound-healing efficacy.[26] The effect was studied in three different experimental wound models. Animals were first wounded under pentobarbitone (40mg/Kg/IP) anesthesia (administered with ether) to bear either incision/ or excision/ dead space wound. The crude extract was then given in the dose of 500 mg/Kg/orally (once daily) up to 10 days (incision and dead space wound) or until complete healing (excision wound) and the tensile strength was measured on the 10^{th} day. In the excision wound model, the crude extract showed significant ($P<0.001$) reduction on the epithelisation period (17.22±0.46 days) compared to that of the control (21±0.1 days). Again, significant inhibition in the rate of wound contraction was also noted on the 4^{th}, 8^{th}, 10^{th} and 12^{th} days whereas significant enhancement ($P<0.001$) in wound contraction (97.59±0.64%) was shown from the 16^{th} day. Effects of crude extract on other wound models were reported to be insignificant.[26]

Antioxidant activity

Suksamrarn *et al.*[27] reported significant antioxidant activity of chloroform extract (aerial parts) of *L. geoffrayi*. This extract led to the isolation of two pentaoxygenated flavones — nevadensin (**2**) and isothymusin (**5**), of which only the latter exhibited antioxidant activity against the radical scavenging ability of 1,1-diphenyl-2-picrylhydrazyl (DPPH) having the IC_{50} value of 7.7 µg/mL. The efficacy is almost comparative with the standard antioxidant compound 2,6-di-(tert-butyl)-4-methylphenol (BHT, IC_{50} =5.7 µg/mL).

It is interesting to note that isothymusin while shows strong antioxidant property, nevadensin cannot. This contrasting difference may be explained on the basis of structure/activity relationship. The free 4'-hydroxy group in isothymusin **(5)** molecule exerts delocalisation with the 4-keto group after the 4'-hydrogen is removed. The *p*-hydroquinone nature of the A-ring may contribute to the relatively greater antioxidant activity of the compound. It may also be mentioned that the free 7-hydroxyl group of nevadensin does not exhibit any radical scavenging activity by same mechanism to that of the free 4'-hydroxyl group observed for isothymusin. This may be due to the steric hindrance developed due to the two adjacent methoxyl groups, although such effect is not observed in case of BHT. The antioxidant efficacy of isothymusin, isolated from other sources was also established by Wang *et al.*[81] and also by Kelm *et al.*[82]

Methanolic extract of *L. aromatica* was found to show antioxidant potential against DPPH radical.[75] In this experiment α-tocopherol has been used as standard. The investigators reported EC_{50} value of 550.5 ± 12.2 µg extract per mg DPPH and concluded that presence of phenolic compounds in the extract may be responsible for this activity. Ethanol extract of *L. aromatica* was also reported to have potential antioxidant activities against DPPH radical and FRAP antioxidant assays.[77] The antioxidant efficacies of methanol extract, essential oil as well as isolated compounds (from essential oil) of *L. aromatica* were investigated *in vitro* against DPPH and nitric oxide (NO) radical scavenging as well as anti-lipid peroxidation activity.[67] The results showed that methanol extract and essential oil were active in all such tests-- the methanol being more potent than essential oil. Eugenol (**125**) was found to be active against DPPH radical. Although, eugenol (**125**) and γ-terpinene (**65**) exhibited anti-lipid peroxidation, the authentic compounds were almost inactive against NO scavenging assay.[67] Aqueous extract of *L. aromatica* exhibited *in vitro* antioxidant activity against DPPH assay, the ferric reducing FRAP assay, dihydrofluorescein (DHF) assay, and also found to inhibit NO production in RAW 264.7 macrophages.[83] The aqueous extract showed significant free radical scavenging activity and ability to scavenge intracellular oxygen radical in DHF assay compared to standard used and also inhibited NO production (**Table 7.5**). In another investigation, aqueous, methanol, ethanol and acetone extract of freeze dried *L. aromatica* were assessed *in vitro* for determining antioxidant activity, total phenolic content and total flavonoid content.[84] The pure ethanol extract showed the highest phenolic (40.5 mg GAE/gm extract) and flavonoid content (31.11 mg QCE/gm extract), highest

reducing power as well as DPPH radial scavenging activity. The investigator concluded that *L. aromatica* may be applied in dietary applications to reduce oxidative stress.[84]

Table 7.5: Antioxidant activity and total antioxidant capacity (FRAP assay) of *L. aromatica* aqueous extract

IC_{50} value against DPPH assay (µg/mL)	IC_{50} value against DHF assay (µg/mL)	IC_{50} value to inhibit NO formation (µg/mL)	Ascorbic acid equivalence (µg/mg extract)
10.78 ± 0.31	17.52 ± 2.57	553 ± 51	188 ± 7

Cytotoxic activity

Nevadensin (**2**) isolated from the plant *L. conferta* was reported to display moderate cytotoxic activity[34] the test compound showed 100% cytotoxicity at a concentration of 75µg/mL both in Dalton's lymphoma ascites tumour and Ehrlich ascites tumour (using Swiss albino mice model). The compound was found to be more effective than wogonin that showed only 24.1% cytotoxicity in both the tumours at the same concentration.[26] This findings support the view of Dong *et al.* that the methoxylated flavones possess moderate cytotoxic activity.[85] Methanol and aqueous extracts of *L. indica* were assessed for their cytotoxic activities against three human cancer cell lines – gastric adenocarcinoma cells (AGS, ATCC: CRL-1739), colorectal adenocarcinoma cells (HT-29, ATCC: HTB-38) and breastductal carcinoma cells (MDA-MB-435S, ATCC: HTB-129) as well as normal mouse fibroblast cells (NIH/3T3, ATCC: CRL-1658).[86] The aqueous extract was found to be inactive against normal mouse fibroblast cells and colorectal adenocarcinoma cells but active against gastric adenocarcinoma cells and breastductal carcinoma cells with IC_{50} values of 2.24 and 1.25 mg/mL, respectively. On the other hand, methanol extract showed moderate activity against normal mouse fibroblast cells and gastric adenocarcinoma cells (IC_{50}>2.5 mg/mL but potent against colorectal adenocarcinoma cells and breastductal carcinoma cells having IC_{50} value of 2.19 and 1.24 mg/mL, respectively.[86]

Anthelmintic activity

From the studies of Reddy group[26] with the essential oil of *L. conferta* on a variety of worms, it appears that the oil might be used as a potent and effective antidote against such parasites. The oil exhibited dose-dependent antihelmintic activity against the test organisms, and in each case the oil was found to be more effective than the standards used. The experimental results are tabulated below (**Table 7.6**):

Table 7.6: Essential oil of *L. conferta* against earth worm model[26]

Worms	Dose(mg/mL)	Time required for death (min.)
Earthworm	1.7	142
Round worm	2.0	240
Tape worm	1.7	55

Vascular protective activity

The aqueous extract of *L. aromatica* was reported to exhibit *in vivo* vascular protective potential against male Sprague-Dawley rats. It was reported that hemodynamic status of phenylhydrazine (PHZ) induced rats is improved by controlling PHZ induced severe hemolysis and hemodynamic disturbances on administration of aqueous extract at a dose of 1 g/kg per day.[83] Again, the plant extract is found to restore vascular responsiveness to bradykinin, acetylcholine, and phenylephrine in experimental rats. Moreover, loss of blood reduced glutathione is prevented and the formation of plasma malondialdehyde, plasma NO metabolites as well as blood superoxide anion are suppressed by the extract. It was finally concluded that presence of antioxidant constituents in the plant extracts accounting for their potential roles in protection of vascular dysfunction.[83]

Diuretic Activity

Aqueous as well as alcoholic extracts of *L. rugosa* leaves were found to show promising diuretic activity as dose dependent manner.[73] The investigators reported that urine volume and excretion of K^+ ion as compared to normal saline are increased after six hour administration of the extracts.

Effect on Guinea-pig ileum

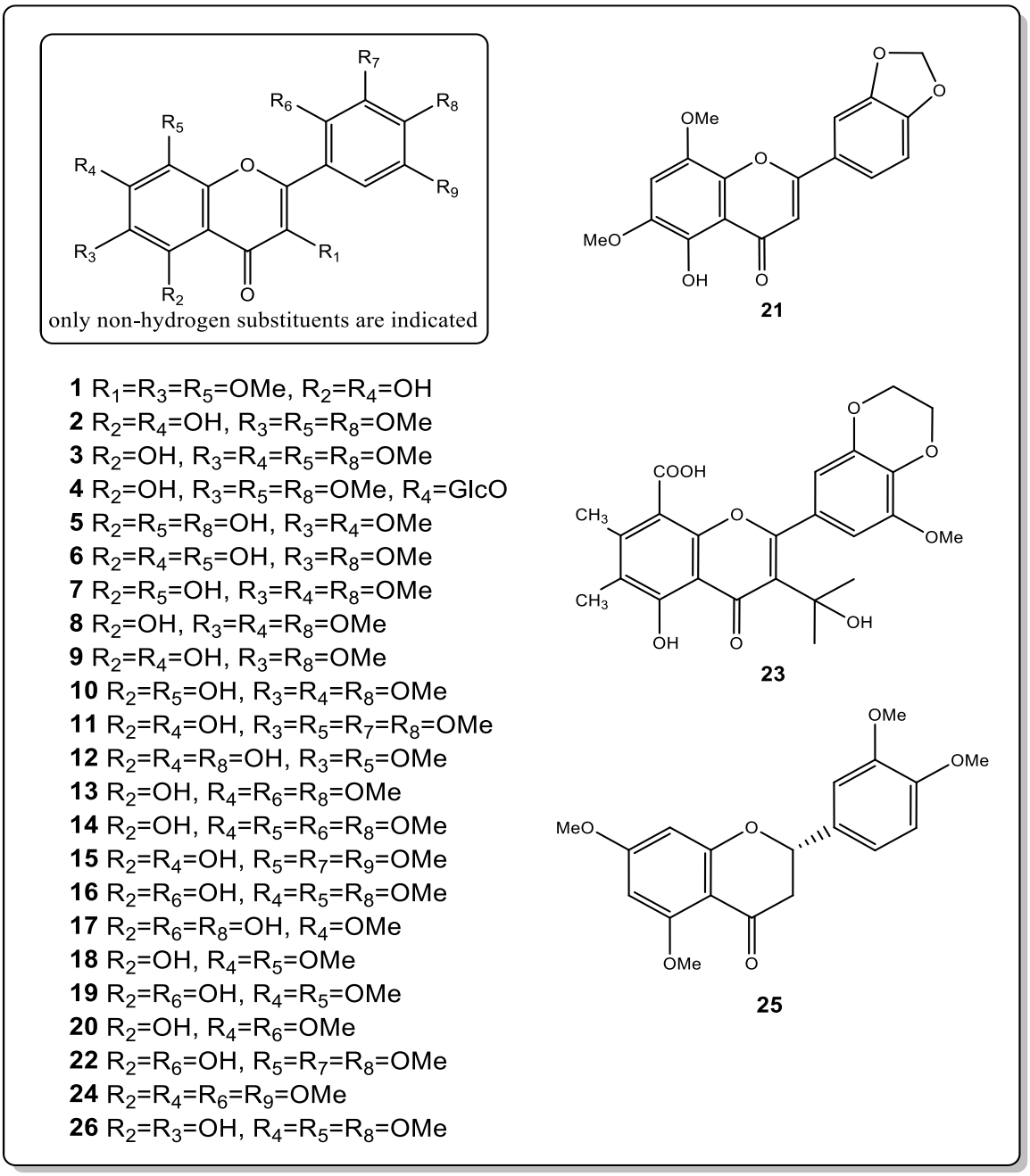
A research group[87] investigated, following the method of Miura *et al.*,[88] the effect of *L. rugosa* aqueous extract on guinea-pig ileum and found that the extract at the concentration of 10^{-4} g/mL enhanced the concentration induced by histamine used as stimulant.[87]

Hypotensive activity

Nevadensin (**2**), a flavonoid constituent of *L. rugosa*, was found to exhibit hypotensive effect on both normotensive and spontaneous hypertensive rats under pentobarbital anesthetization.[35]

MATERIALS AND METHODS

The phytochemical constituents isolated and identified from *Limnophila genus*, pharmacological activities exhibited by the crude plant extracts as well as by the isolated phytochemical constituents were searched across the Science Direct databases and Medline (National Library of Medicine). All data were updated in September 2014, using the search-terms *Limnophila species*, phytochemical constituents of *Limnophila species*, biological activities and pharmacological activities or properties of *Limnophila species* as keywords. In addition, the reference lists of all papers collected were thoroughly reviewed.



1 R_1=R_3=R_5=OMe, R_2=R_4=OH
2 R_2=R_4=OH, R_3=R_5=R_8=OMe
3 R_2=OH, R_3=R_4=R_5=R_8=OMe
4 R_2=OH, R_3=R_5=R_8=OMe, R_4=GlcO
5 R_2=R_5=R_8=OH, R_3=R_4=OMe
6 R_2=R_4=R_5=OH, R_3=R_8=OMe
7 R_2=R_5=OH, R_3=R_4=R_8=OMe
8 R_2=OH, R_3=R_4=R_8=OMe
9 R_2=R_4=OH, R_3=R_8=OMe
10 R_2=R_5=OH, R_3=R_4=R_8=OMe
11 R_2=R_4=OH, R_3=R_5=R_7=R_8=OMe
12 R_2=R_4=R_8=OH, R_3=R_5=OMe
13 R_2=OH, R_4=R_6=R_8=OMe
14 R_2=OH, R_4=R_5=R_6=R_8=OMe
15 R_2=R_4=OH, R_5=R_7=R_9=OMe
16 R_2=R_6=OH, R_4=R_5=R_8=OMe
17 R_2=R_6=R_8=OH, R_4=OMe
18 R_2=OH, R_4=R_5=OMe
19 R_2=R_6=OH, R_4=R_5=OMe
20 R_2=OH, R_4=R_6=OMe
22 R_2=R_6=OH, R_5=R_7=R_8=OMe
24 R_2=R_4=R_6=R_9=OMe
26 R_2=R_3=OH, R_4=R_5=R_8=OMe

Fig. 1: Structures of flavonoids from *Limnophila*

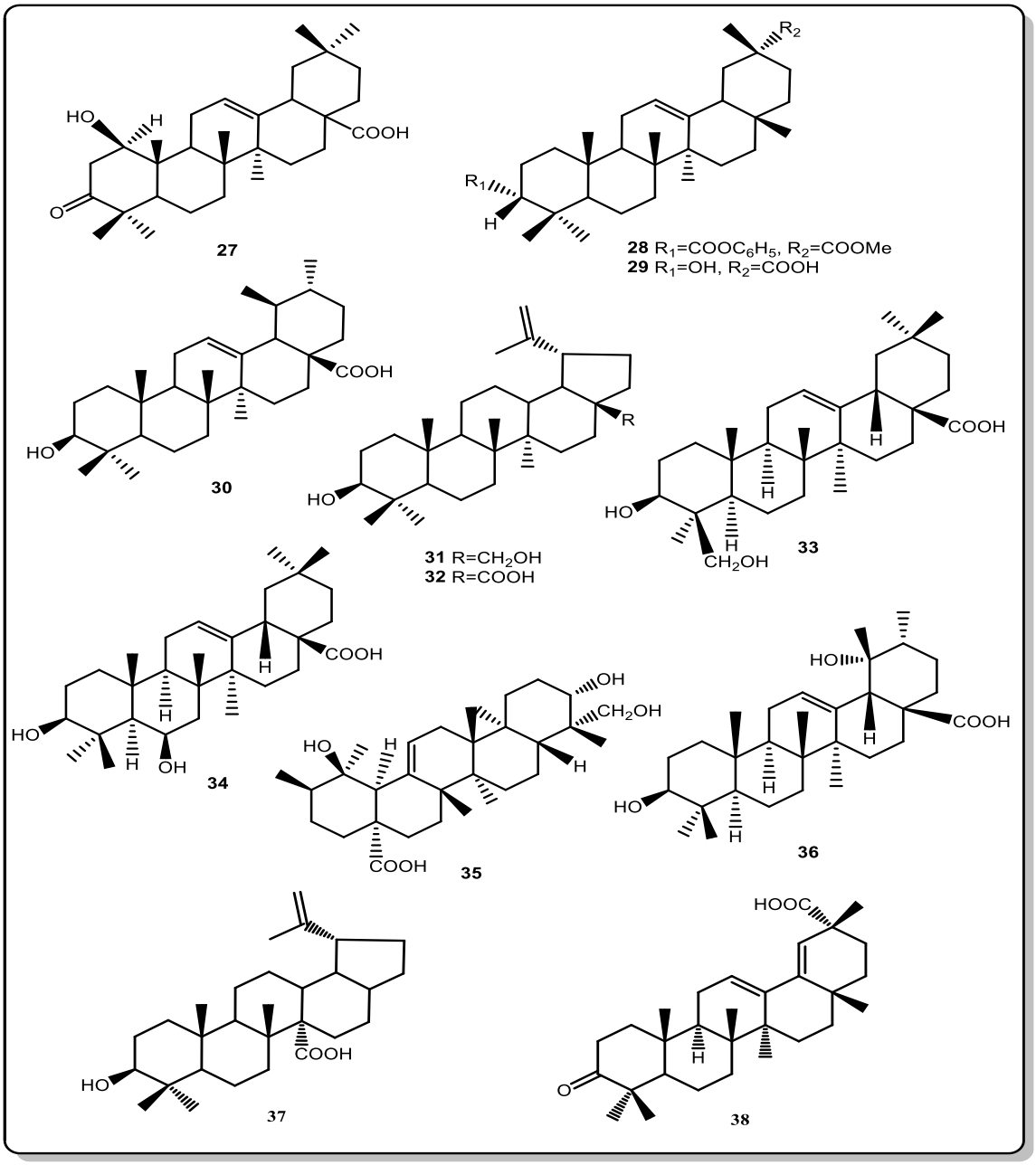


Fig. 2: Structures of terpenoids from *Limnophila (Cont.....)*

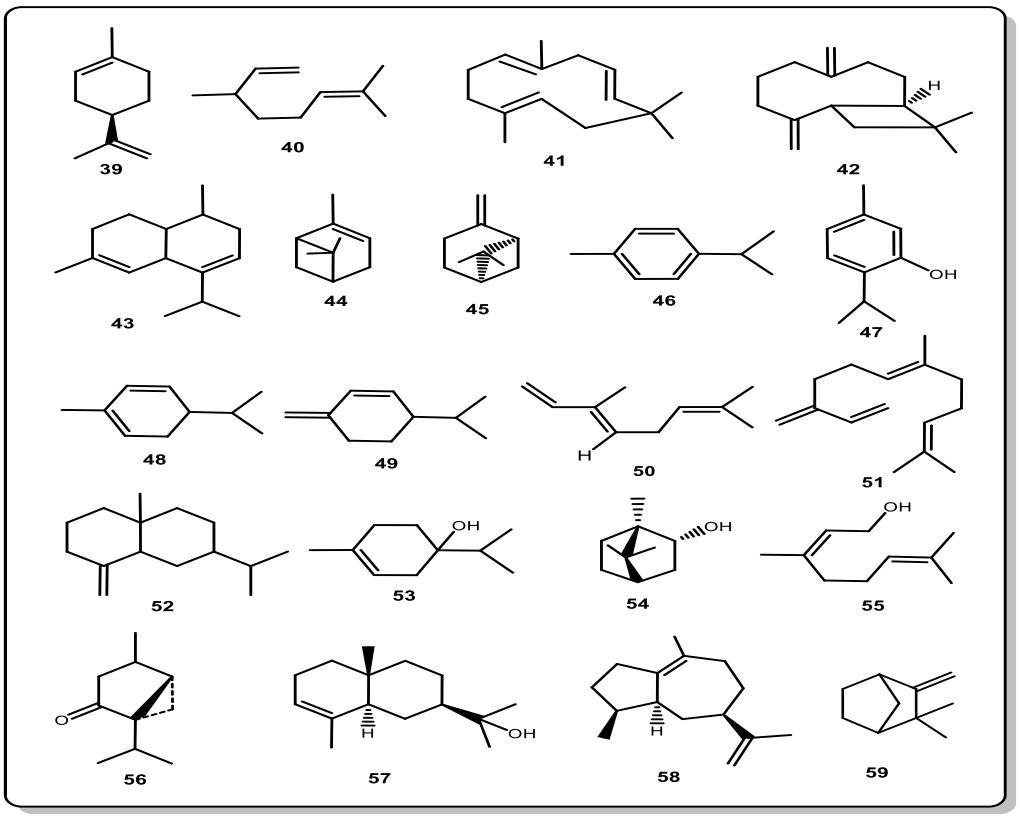


Fig. 2: Structures of terpenoids from *Limnophila (Cont.....)*

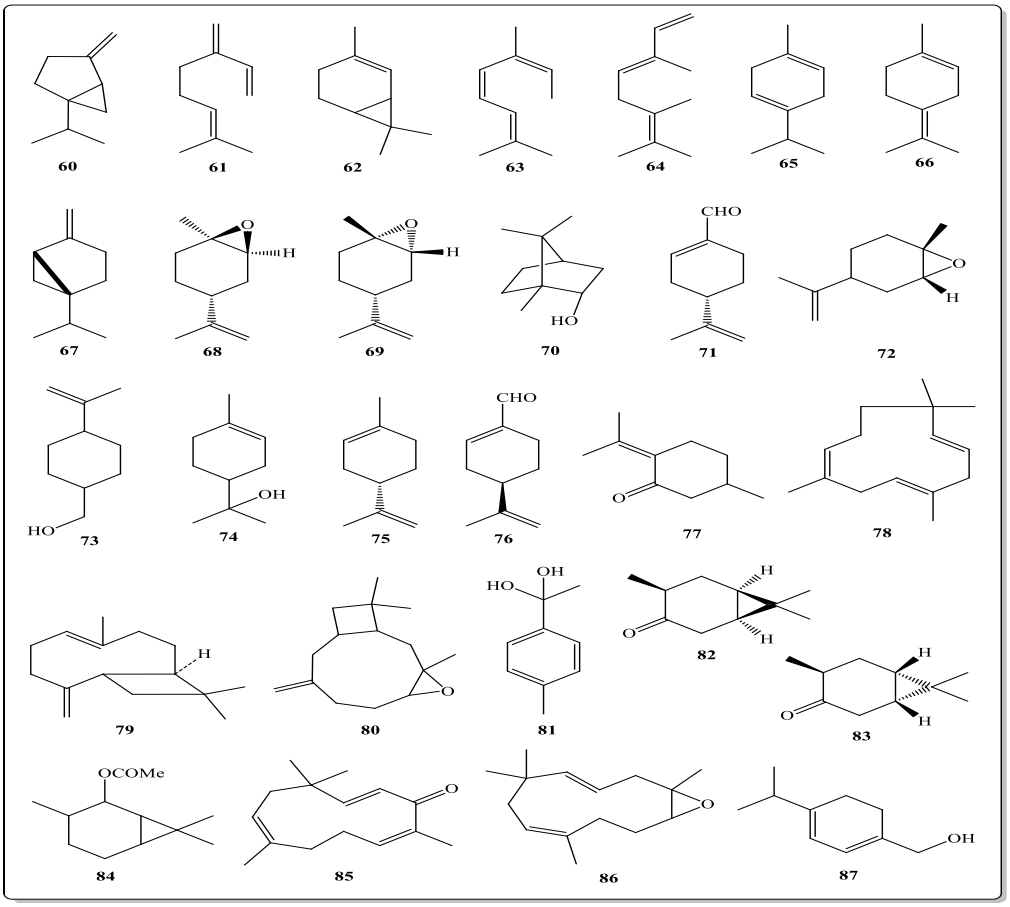


Fig. 2: Structures of terpenoids from *Limnophila*

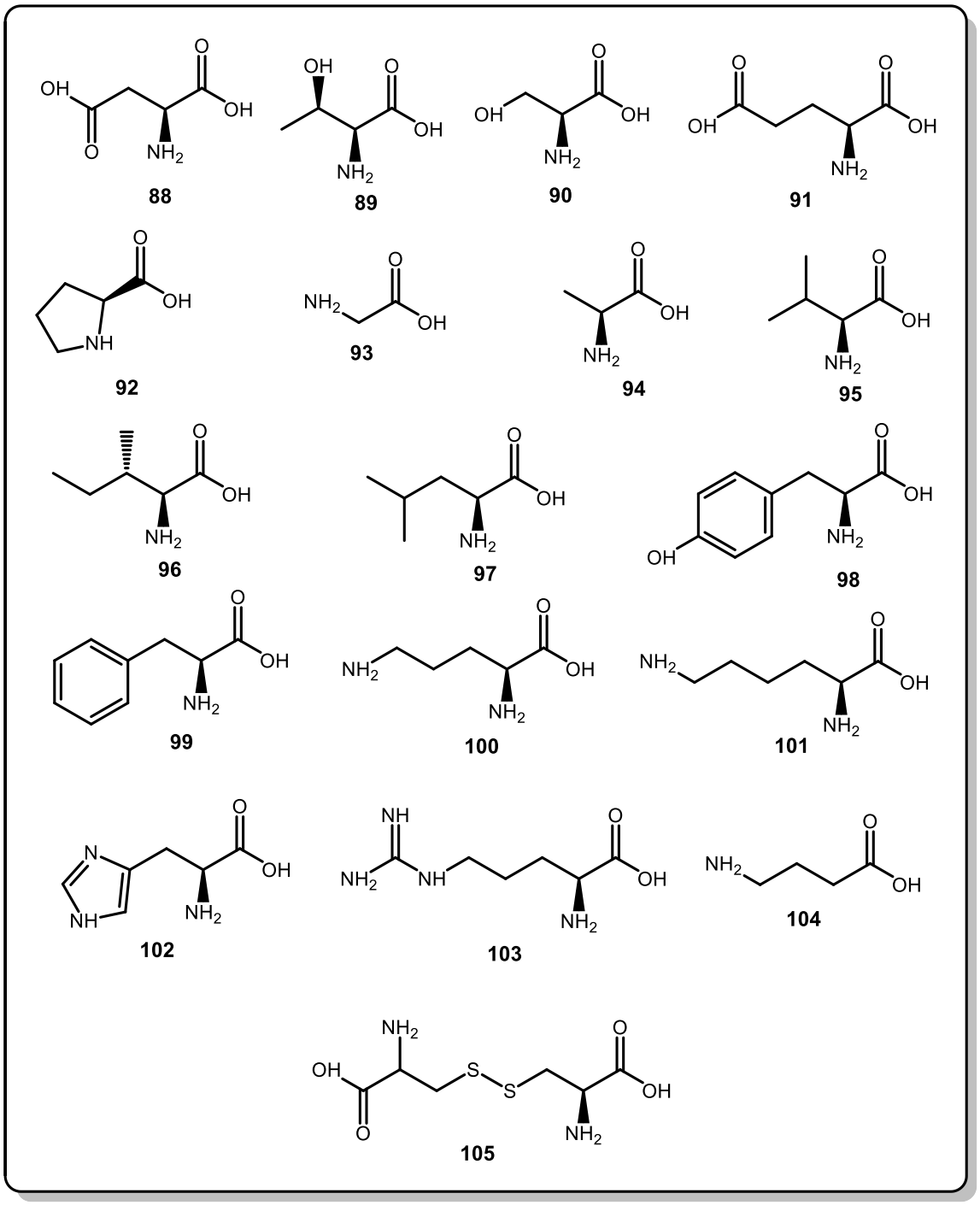


Fig. 3: Structures of amino acids from *Limnophila*

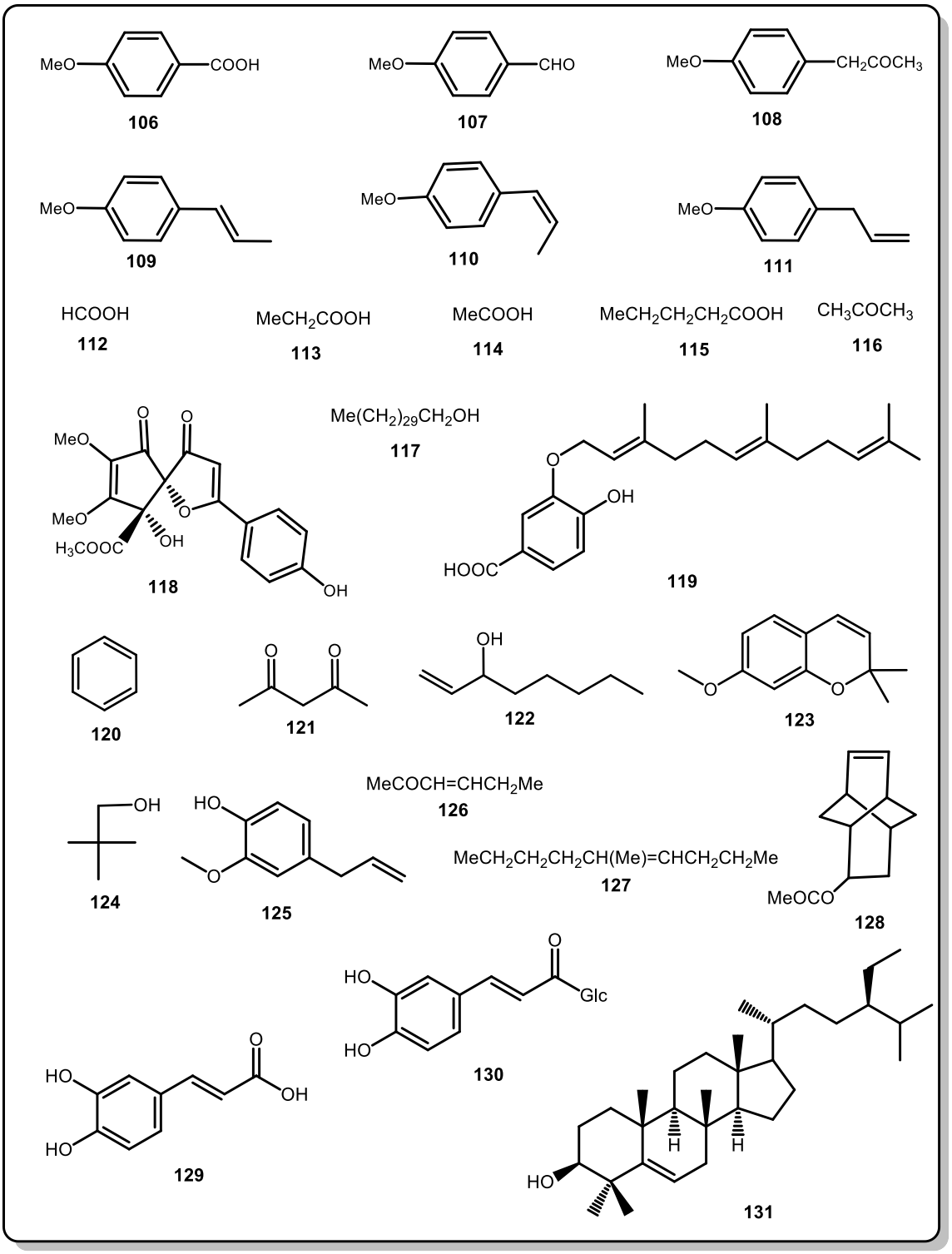


Fig. 4: Structures of miscellaneous compounds from *Limnophila*

CONCLUDING REMARKS

Limnophila plants are widely distributed world-wide, and find immense applications in traditional systems of medicine in many countries. Although some works on the chemical and pharmacological aspects of these plants have already been done, a major portion remains

unexplored. This present resume is an attempt to compile an up-to-date literature covering its botany to ethnobotany, biological and pharmacological studies as well as phytochemicals as reported so far from this important genus. The goal of this review is to grow interests among the researchers working in this direction to undertake more systematic research works on this genus toward the searches for 'promising leads' in modern drug development processes.

LIST OF ABBREVIATIONS

BHT : 2,6-di-(tert-butyl)-4-methylphenol
COX-1 : cyclooxygenase-1
COX-2 : cyclooxygenase-2
DHF : dihydrofluorescein
DMSO : dimethyl sulfoxide
DPPH : 1,1-diphenyl-2-picrylhydrazyl
EC_{50} : half maximal effective concentration
FRAP : ferric reducing antioxidant power
IC_{50} : half maximal inhibitory concentration
MBC : minimal bactericidal concentration
MIC : minimal inhibitory concentration
NO : nitric oxide
PHZ : phenylhydrazine

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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