REVIEW ARTICLE

Bioactive phytoconstituents and plant extracts from genus *Heliotropium*

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Heliotropium is a genus of herbs and rarely shrubs of family Boraginaceae. *Heliotropium* species have been used in folk medicine for the treatment of gout, rheumatism and as antiseptic, febrifuge, cholagogue, anti-inflammatory and healing agents. The alkaloids mainly pyrrolizidine alkaloids are the main constituents of *Heliotropium* species, which are responsible for several biological activities *viz.* anti-tumoural, anti-microbial, and anti-viral effects. Phenolic compounds, terpenoids, and quinones have also been reported in this genus. The present review summarizes the various biological studies done on the extracts and bioactive phytoconstituents from the plants of the genus *Heliotropium* over the past few decades.

Key words: Biological activities, boraginaceae, *heliotropium*, phytoconstituents, review

INTRODUCTION

Heliotropium is a genus of herbs and rarely shrubs, belonging to family Boraginaceae. These are distributed in the tropical and temperate regions of the world. There are about 300 species in this genus, which are commonly known as heliotropes. About 16 species occur in India.[1,2]

The name "heliotrope" derives from the fact that these plants turn their leaves to the sun. *Helios* is Greek word for "sun", *tropein* means "to turn". Within the family, *H.* species exhibit great variation in many features of biological interest including physiognomy, habitat preferences and morphological traits. Most of species are distributed in tropical and temperate regions in a variety of habitats. Many of heliotropes are weed of cultivated fields, whereas others are characteristically associated with *Acacia radiana*, *Acacia tortilis* and hydro-segetal vegetation in the Middle East.[3]

H. species (Boraginaceae) have been used in folk medicine for the treatment of rheumatism, gout and as febrifuge, antiseptic, cholagogue, anti-inflammatory and healing agents.[4]

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The main constituents of *H.* species, pyrrolizidine alkaloids (PAs), are responsible for various biological activities, including anti-tumoural, anti-microbial, and anti-viral effects.[5-8] Phenolic compounds, terpenoids, and quinones are the various phytoconstitutes reported in this genus.[9-12]

The present paper summarizes the various biological studies done on the extracts and bioactive phytoconstituents [Figure 1] from the plants of the genus *Heliotropium* over the past few decades.

Biological Studies

Anti-Feedant Activity

Bioassays of the alkaloid extract and new saturated pyrrolizidine monoester alkaloids viz. 3′-acetyltrachelanthamine (1), floridine (2), floridinine (3), floridimine (4) and heliovicine (5) from *H. floridum* showed that 3′-acetyltrachelanthamine is a strong anti-feedant, with low toxicity against *Leptinotarsa decemlineata* and a moderate anti-fungal agent against *Fusarium monoliforme;* floridinine only showed the anti-fungal effect. This is the first report of an anti-feedant PA acting on this insect.[13]

Anti-Inflammatory Effect

The anti-inflammatory activity of crude extract of *H. strigosum* and its subsequent solvent fractions was evaluated using carrageenan-induced oedema and xylene-induced ear oedema animal models at 50, 100, and 200 mg/kg intraperitoneally. The results revealed marked attenuation of oedema induced by carrageenan injection in a dose-dependent manner.

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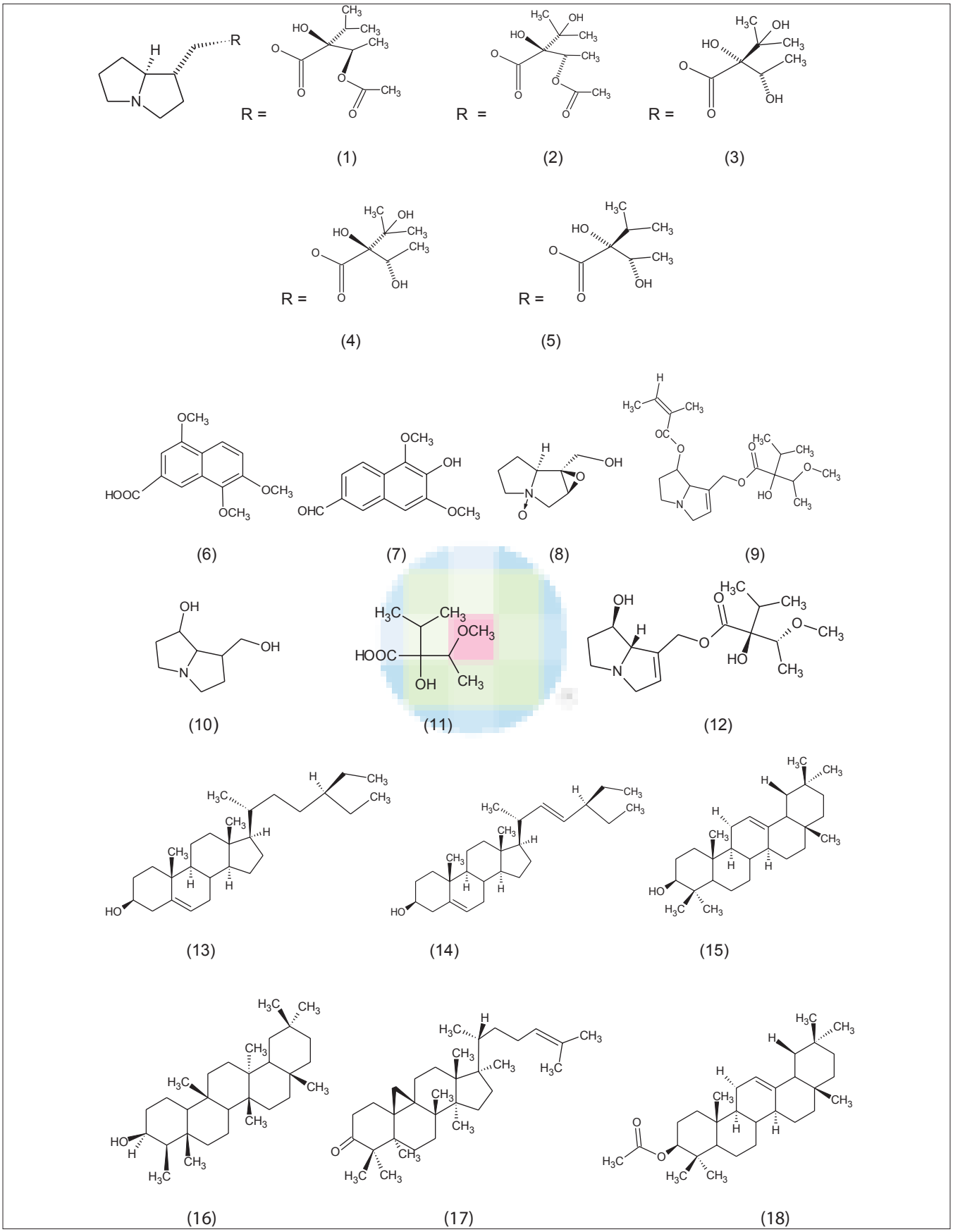

Figure 1: Phytoconstituents from *Heliotropium* spp. (cont.)

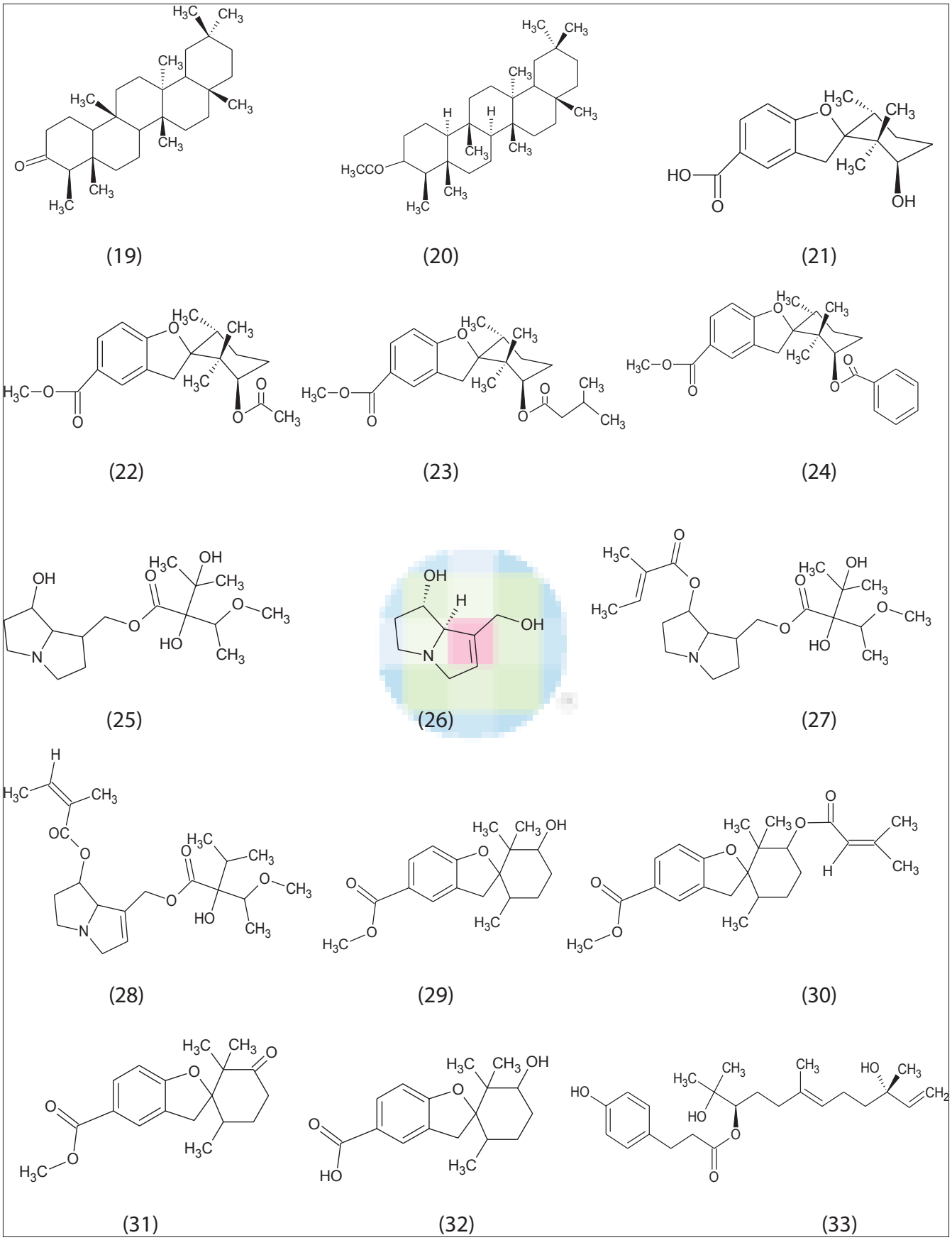

Figure 1: Phytoconstituents from *Heliotropium* spp.

The ethyl acetate fraction was most dominant with 73.33% inhibition, followed by hexane fraction (70.66%). When the extracts were challenged against xylene-induced ear oedema, again ethyl acetate and hexane fractions were most impressive with 38.21 and 35.77% inhibition, respectively. The study indicated that various extracts of *H. strigosum* possessed strong anti-inflammatory activity in animal models.[14]

The anti-inflammatory effect of *H. indicum* leaf was found to posses significant in carrageenan-induced hind paw oedema and cotton pellet granuloma models of inflammation.[15]

The anti-inflammatory effect of *H. ovalifolium* was identified in its ability to inhibit specific cytokines, interleukin-6 (IL-6). Further, bioassay guided fractionation, identified two compounds 4,7,8-trimethoxy-naphthalene-2-carboxylic acid (6) and 6-hydroxy-5,7-dimethoxy-naphthalene-2-carbaldehyde (7) with an IC_{50} of 2.4 and 2.0 mM for IL-6 inhibition and an IC_{50} of 15.6 and 7.0 mM for tumour necrosis factor - alpha (TNF-α) inhibition in THP-1 cells.[16]

Anti-Inflammatory and Antinociceptive Activities

Chloroform extract of *H. indicum* was investigated for anti-inflammatory and antinociceptive activities in experimental animal models. The extract (150 mg/kg b.w.) showed maximum inhibition (80.0%) and (82.79%) antinociception on carrageenan-induced rat paw oedema and hot plate model in male Swiss albino mice, respectively.[17]

Antimicrobial Activity

Petroleum ether and chloroform fractions from the ethanol extract and five PA *viz*. subulacine-N-oxide (8), angeloyl heliotrine (9), retronecine (10), heliotric acid (11) and heliotrine (12) isolated from *H. subulatum* were tested for their antimicrobial activity against bacteria (*Escherichia coli, Streptococcus pneumoniae, Bacillus subtilis, B. anthracis, Staphylococcus aureus*) and fungi (*Aspergillus fumigatus, A. niger, Rhizoctonia phaseoli and Penicillium chrysogenum*). The chloroform fraction exhibited greater activity against *E. coli*, whereas petroleum ether fraction demonstrated better effect against *P. chrysogenum*. Among the isolated compounds, 7-angeloyl heliotrine possesses maximum activity *vs*. *E. coli* and *P. chrysogenum*.[7]

The *in vitro* antifungal activity of aqueous, ethanol, chloroform, petroleum ether, and residue extracts from 10 indigenous Bahraini plants including *H. curassavicum* L. used in folk medicine for the treatment of various diseases is reported. The diffusable metabolites of *H. curassavicum* L. demonstrated marked inhibitory effects against *P. citrinum* then followed by *Candida albicans*.[18]

Seven sterols and triterpenoids *viz*. β-sitosterol (13), stigmasterol (14), β-amyrin (15), friedelan-β-ol (16), cycloartenone (17), β-amyrin acetate (18) and friedelin (19) were isolated from *H. ellipticum* and tested for their antimicrobial activity against bacteria and fungi strains using disc diffusion method. Cycloartenone and friedelin were found to possess the widest spectrum and highest level of antimicrobial activity, comparable with that of the reference antibiotics.[19]

Isolated triterpenoid from hexane extract of *H. marifolium viz*. β-sitosterol (13), stigmasterol (14), β-amyrin (15), friedelan-β-ol (16), cycloartenone (17), β-amyrin acetate (18), friedelin (19), epifriedenyl acetate (20) and reference antibiotics (gentamycin/mycostatin) were tested against selected pathogenic bacteria and fungi, e.g. *E. coli*, *Staphylococcus aureus*, *Aspergillus niger* and *P. chrysogenum*. The results showed that friedelan-3β-ol was the most active against selected bacteria and fungi, namely *S. aureus* (17; 1.07), *K. pneumoniae* (17; 1.06) and *A. flavus* (10; 1.11), whereas β-sitosterol was active against *E. coli* (16; 1.06). β-amyrin acetate showed potent activity against *P. chrysogenum* (09; 1.12) and stigmasterol had mild activity compared with β-amyrin acetate against *P. chrysogenum*.[20]

The antimicrobial properties of the isolated compounds 3′-hydroxy- 2′,2′,6′-trimethyl-3*H*-spiro[1-benzofuran-2,1′-cyclohexane]-5-carboxylic acid (21), methyl 3′- acetyloxy-2′,2′,6′- trimethyl-3*H*-spiro[1-benzofuran-2,1′-cyclohexane]-5-carboxylate (22), methyl 3′-isopentanoyloxy-2′,2′,6′-trimethyl- 3*H*-spiro[1-benzofuran-2,1′-cyclohexane]-5-carboxylate (23) and methyl 3′- benzoyloxy-2′,2′,6′- trimethyl -3*H*-spiro[1-benzofuran-2,1′-cyclohexane]-5-carboxylate (24) from *H. filifolium* were proved to be active against Gram positive, but inactive against Gram negative bacteria.[21]

Anti-microbial activity of the essential oil isolated by hydrodistillation of *H. europaeum* were tested on *B. subtilis* PTCC 1023, *Staphylococcus aureus* PTCC 1112, *E. coli* PTCC 1330, *Salmonella typhi* PTCC 1639, *Aspergillus niger* PTCC 5011, and *C. albicans* PTCC 5027 by diffusion method using filter paper disk (6 mm). The result showed the significant activity against *B. subtilis* and *Salmonella typhi*.[22]

Alcoholic extract of *H. indicum* was found to posses promising anti-microbial activity against four strains each of Gram positive and Gram negative bacteria, three fungi and two yeast by agar cup plate diffusion method.[23]

Anti-microbial activity of different extracts (chloroform, ethyl acetate, methanol, water) of the *H. marifolium* was assessed by standard dilution test using Mueller Hinton agar (MH) medium. The findings showed potential anti-microbial

properties (minimum inhibitory concentration (MIC) =133.3 µg/ml) of the extracts against the organisms tested.[24]

The alcoholic extract of *H. indicum* was found to possess dose- dependent antimicrobial activity against selected bacteria, fungi and yeast.[25]

The sequential extracts (petroleum ether, benzene, chloroform and ethanol) of aerial parts of *H. ellipticum* exhibited weak antimicrobial activity, however, its alkaloid-rich fractions demonstrated pronounced activity.[26]

The PA europine (25), heliotridine (26), lasiocarpine (27) and lasiocarpine-N-oxide isolated from *H. ellipticum* showed positive antimicrobial activity against selected pathogenic bacteria and fungi.[27]

Antineoplastic and Antiviral Activities

The phytochemical investigation of *H. subulatum*, guided by bioassay, led to the isolation of heliotrine (12), 7-angeloyl heliotrine (28), retronecine (10), subulacine and subulacine- *N*-oxide (8). Antineoplastic, cytotoxic and antiviral activities of ethanol, hexane, dichloromethane crude extracts and isolated PA have been screened by packed cell volume and plaque inhibition methods. The 7-angeloyl heliotrine and retronecine showed activity at 5mg/kg/day of 41.7% and 38.6% inhibition against Sarcoma 180. The hexane extract (3 mg/ml) and 7-angeloyl heliotrine (10 and 5 mg/ml) showed selective cytotoxicity against Chinese hamster V79 cells. The ethanol and hexane crude extract showed significant antiviral activity to *Coxsackie, Poliomyelitis* and *Measles* at 500 and 100 mg/ml concentrations, whereas heliotrine and 7-angeloyl heliotrine possess activity against *Poliomyelitis* and *Vesicular stomatitis* at a concentration of 10 mg/ml.[6]

Antioxidant Activity

Relationships between the structural characteristics of flavonoids isolated from the resinous exudate of *H. sinuatum* and their anti-oxidant activity were studied. Results show that studied flavonoids can be divided into two sets based on their activity. It has been found that anti-oxidant activity depends both on substitution pattern of hydroxyl groups of the flavonoid skeleton, where the most active compounds would be those having hydroxyl groups at C-4′ and/or C-3′, for which the lowest values of dehydrogenation (DH) were obtained and the presence of an unsaturation at the C2-C3 bond. A good tendency between DH of dehydrogenation and anti-oxidant activity was established.[28]

The antioxidant activity of the phenolic compounds and resin viz. filifolinol (29), naringenin and 3-oxo-2-arylbenzofuran derivative 3) from *H. sclerocarpum* was evaluated using the bleaching of diphenylpicrylhydrazy (DPPH) radical method and expressed as fast reacting equivalents (FRE) and total reacting equivalents (TRE). The values of FRE and TRE of extract are superior in comparison with those obtained for the pure compounds. This indicates that the resin offers instantaneous protection to the plant and also on the long term. This can be the result of some form of synergism of their components.[29]

Antioxidant and Anti-Hyperlipidemic Effects

The potential role of the methanolic extract of *H. zeylanicum* in the treatment of diabetes along with its antioxidant and anti-hyperlipidemic effects was studied in streptozotocin-induced diabetic rats. Oral administration of extract 150 and 300 mg/kg/d for 14 days significantly decreased the blood glucose level and considerably increased the body weight, food intake, and liquid intake of diabetic-induced rats. The extract significantly decreased thiobarbituric acid reactive substances and significantly increased the reduced glutathione, superoxide dismutase and catalase in streptozotocin-induced diabetic rats at the end of 14 d of treatment. The study also showed the antihyperlipidemic potential of the extract.[30]

Antiplasmodial and Antitrypanosomal Activities

The antiplasmodial and antitrypanosomal activities of the methanol extracts of 42 plants including *H. zeylanicum* collected from the Kingdom of Saudi Arabia and some fractions obtained thereof were evaluated. The antiplasmodial activity was tested *in vitro* against chloroquine-resistant strain (K1) and sensitive strain (FCR3), and the antitrypanosomal activity was tested *in vitro* against *Trypanosoma brucei brucei* GUTat 3.1 strain. For host cells, the cytotoxicity of the active extracts was also evaluated against the MRC5 human cell line. Extracts of *H. zeylanicum* demonstrated good anti-plasmodial activity (IC50 < 12.5 and > 1.56 µg/ml). As for the anti-trypanosomal activity and cytotoxicity, extract of *H. zeylanicum* showed moderate activity with IC50 of 4.6µg/ml and 13 µg/ml, respectively.[31]

Anti-Plasmodial Properties

Plants traditionally used in India to treat fever or malaria were examined *in vitro* for anti-plasmodial properties against *Plasmodium falciparum*. The extract of root of *H. europaeum* L. *var*. *lasiocarpum* showed significant activity along with 30 other extracts out of 80 tested extracts.[32]

Twelve plant species including *H. indicum* L. (Boraginaceae), traditionally used in Benin for the treatment of malaria was evaluated in order to validate their use. The results showed that extracts of *H. indicum* L. did not reveal any anti-plasmodial activity in this study. As this plant is used for hyperthermias or colics, which are two symptoms of malaria, this could explain its use as adjuvant in mixture remedies.[33]

Antiproliferative Activity

Ethanolic extract of *H. indicum* showed significant anti-proliferative activity against SKBR3 human breast adenocarcinoma cell line using MTT assay.[34]

Antituberculosis Activity

The volatile oil isolated from the aerial parts of *H. indicum* was evaluated for anti-tuberculosis activity and the results showed significant anti-tuberculosis activity against *Mycobacterium tuberculosis* H37Ra in the Alamar blue assay system with an MIC of 20.8 µg/ml.[35]

Anti-Viral Activity

Infectious pancreatic necrosis is a disease caused by a birnavirus affecting several wild and commercial aquatic organisms. This infectious disease results in significant losses in the farming industry and therefore effective therapeutic agents are needed to control outbreaks caused by this pathogen. Thus, *in vitro* anti-viral effect of a group of natural compounds (geranyl aromatic derivatives) *viz*. filifolinol (29), filifolinyl senecionate (30), filifolinone (31) and filifolinoic acid (32) isolated from the resinous exudates of the plant *H. filifolium* (Heliotropiaceae), semi-synthetics compounds obtained from them, and the resinous exudates was evaluated on CHSE-214 cell line infected with infectious pancreatic necrosis virus (IPNV) using a virus plaque inhibition assay at various concentrations. The compound ester filifolinyl senecionate was found to be the best anti-viral with EC_{50} 160 mg/ml and a cytotoxic concentration required to reduce cell viability by 50% up to 400 mg/ml. Further, the influence of ester filifolinyl senecionate on the viral RNA synthesis was evaluated in order to obtain information about the mechanism of the anti-viral action. This compound produced inhibition of the synthesis of viral genomic RNA, suggesting that the ester could be interacting with the viral RNA during the viral cycle. Additionally, a preliminary study of the interaction between ester and a sample of single-stranded RNA showed that the ester formed hydrogen bonds mainly with nitrogenous bases but not with ribose and phosphate. These results proposed that the ester filifolinyl senecionate is a good candidate for use as antiviral therapy for IPN virus in salmon fry.[36]

Histo-Gastroprotective Activity

H. indicum is used locally in Nigeria to treat ailments such as ulcer and fever. The histo-gastroprotective activity of aqueous extract of *H. indicum* was evaluated in Wistar rats, where ulceration was induced *via* the oral administration of 80mg/kg/bodyweight of indomethacin. The result showed that the aqueous extracts of the dried leaves of *H. indicum* have dose-dependent histo-gastroprotective effects.[37]

Immunostimulant Activity

The immunostimulant activity of terpenoid derivatives, filifolinone (31) isolated from species of the Heliotropium genus were evaluated *in vitro* using the SHK-1 cell line derived from leucocytes of salmon head kidney and *in vivo* in Atlantic salmon. The results showed that filifolinone increases the levels of expression of pro-inflammatory and anti-inflammatory cytokines. This suggests that filifolinone is a potential alternative immunomodulator for veterinary purposes.[38]

Inhibitory Activities

Aqueous extract of *H. foertherianum* leaves and rosmarinic acid, isolated compound were evaluated for its effects against a Pacific ciguatoxin (P-CTX-1B) in the neuroblastoma cell assay and the receptor-binding assay. The results showed inhibitory activities against a P-CTX-1B in the tested bioassays and confirm the potential of *H. foertherianum* in the treatment of Ciguatera Fish Poisoning.[39]

Nephroprotective Effect

The nephroprotective effect of methanolic extract of *H. eichwaldi* (MHE) was evaluated in mice against cisplatin-induced acute renal damage. The various parameters such as blood urea nitrogen, serum creatinine, malondialdehyde, and catalase and superoxide dismutase activities were analysed. The results showed that MHE can be considered a potential candidate for protection of nephrotoxicity induced by cisplatin.[40]

Plant-Defensive Properties

The new bioactive sesquiterpenoid, megalanthine (33), was isolated from the resinous exudates of *H. megalanthum* and was evaluated for several plant-defensive properties (insecticidal, antifungal, and phytotoxic). The study showed positive biological effects. However, megalanthine was ruled out as a significant plant–plant defence agent because of its lack of stability.[41]

Wound Healing Activity

The ethanolic extracts of *H. indicum* possess significant wound healing activity. Tensile strength results indicate better activity of *H. indicum* on remodelling phase of wound healing.[42]

CONCLUSIONS

In various traditional systems of medicine, different parts of *H.* spp. are used for various human disorders; however, classic traditional system of medicine lacks scientific studies on the plants of the genus. The pharmacological effect of herbs/phytoconstituents [Table 1] described in the review can be applied through

Table 1: Bioactive extracts and phytoconstituents from genus *Heliotropium*

Activity	Plant	Extract/phytoconstituents (s)	Ref.
Anti-feedant activity	*H. floridum var.* latlfolium	Alkaloidal extract 3'-acetyltrachelanthamine Floridine Floridinine Floridimine Heliovicine	13
Anti-inflammatory activity	*H. strigosum*	Ethyl acetate fraction Hexane fraction	14
Anti-inflammatory activity	*H. indicum* L.	Leaf powder	15
Anti-inflammatory activity	*H. ovalifolium* Forssk.	Extract 4,7,8-trimethoxy-Naphthalene-2-carboxylic acid 6-hydroxy-5,7-dimethoxy-naphthalene-2-carbaldehyde	16
Anti-inflammatory and anti-nociceptive activities	*H. indicum* L.	Chloroform extract	17
Anti-microbial activity	*H. curassavicum* L.	Aqueous, Ethanol, Chloroform, Petroleum ether, and Residue extracts	18
Anti-microbial activity	*H. subulatum* Hochst. ex DC.	Petroleum ether Chloroform fractions Subulacine -N-oxide Angeloyl heliotrine Retronecine Heliotric acid Heliotrine	07
Anti-microbial activity	*H. ellipticum* Ledeb.	β-sitosterol Stigmasterol β-amyrin Friedelan-β-ol Cycloartenone β-amyrin acetate Friedelin	19
Anti-microbial activity	*H. marifolium* Koen. ex Retz.	β-sitosterol Stigmasterol β-amyrin Friedelan-3β-ol Cycloartenone β-amyrin acetate Friedelin Epifriedenyl Acetate	20
Anti-microbial activity	*H. filifolium* (Miers) Reiche	3'-hydroxy-2',2',6'-trimethyl-3H-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylic acid Methyl 3'-acetyloxy-2',2',6'-trimethyl-3Hspiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylate Methyl 3'-isopentanoyloxy 2',2',6'-trimethyl-3H-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylate Methyl 3'-benzoyloxy-2',2',6'-trimethyl-3H-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylate	21
Anti-microbial activity	*H. europaeum* L.	Essential oil	22
Anti-microbial activity	*H. indicum* L.	Alcoholic extract	23, 24
Anti-microbial activity	*H. marifolium* Koen. ex Retz.	Chloroform, Ethylacetate, Methanol and Water extracts	25
Anti-microbial activity	*H. ellipticum* Ledeb.	Petroleum ether, Benzene, Chloroform, Ethanol and Alkaloid rich fractions	26
Anti-microbial activity	*H. ellipticum* Ledeb.	Europine Heliotridine Lasiocarpine Lasiocarpine-N-oxide	27

Contd...

Table 1: Contd...

Activity	Plant	Extract/phytoconstituents (s)	Ref.
Anti-neoplastic and anti-viral activities	*H. subulatum* Hochst. ex DC.	Heliotrine 7- angeloyl heliotrine Retronecine Subulacine Subulacine- N-oxide	06
Anti-oxidant activity	*H. sinuatum* Miers.	Flavonoids isolated from the resinous exudates	28
Anti-oxidant activity	*H. sclerocarpum* Phil.	Phenolic compounds and resin	29
Anti-oxidant and antihyperlipidemic effects	*H. zeylanicum* (Burm.f.) Lam	Methanolic extract	30
Anti-plasmodial and anti-trypanosomal activity	*H. zeylanicum* (Burm.f.) Lam	Methanol extracts	31
Anti-plasmodial properties	*H. europaeum L*. var. Lasiocarpum	Ethanolic extract of root	32
Anti-plasmodial properties	*H. indicum* L.	Extracts	33
Anti-proliferative activity	*H. indicum* L.	Ethanolic extracts	34
Anti-tuberculosis activity	*H. indicum* L.	Volatile oil from the aerial parts	35
Anti-viral activity	*H. filifolium* (Miers) Reiche	Filifolinol Filifolinyl senecionate Semi-synthetics derivatives Filifolinone Filifolinoic acid	36
Histo-gastroprotective activity	*H. indicum* L.	Aqueous extract	37
Immunostimulant activity	*H. filifolium* (Miers) Reiche	Filifolinone	38
Inhibitory activities	*H. foertherianum* Diane & Hilger	Aqueous extract	39
Nephroprotective effect	*H. eichwaldi* Stued. ex Dc.	Methanolic extract	40
Plant-defensive properties	*H. megalanthum* J.M. Johnston	Megalanthine	41
Wound healing activity	*H. indicum* L.	Ethanolic extracts	42

modern or alternative herbal medicine approaches. The present review could help the researchers to explore the genus for further authentication of traditional uses of plants of the *H. spp*.

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