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Phytochemicals and therapeutic potentials of *Barleria lupulina*

Hemant A. Sawarkar[1], Ajit Kumar Pandey[2] and Kailas R. Biyani[1]

[1]Department of Pharmacognosy and Phytochemistry, Anuradha College of Pharmacy, Chikhli, Buldhana, Maharashtra 443201, India; [2]Department of Pharmaceutical Chemistry, Shri Shankaracharya Technical Campus, Faculty of Pharmaceutical Sciences, Junwani, Bhilai, Chattisgarh 490020, India.

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Abstract

A well-known herb *Barleria lupulina* is traditionally used as a medicinal and decorative plant. The various parts of this plant are reported to contain a range of phytoconstituents, including terpenes and terpenoidal compounds, iridoid glucosides, iridoid diglucosides, phenylpropanoid glucosides, and phenylethanoid glucosides. Antibacterial, antiarthritic, CNS depressive, anti-osteoporotic, antioxidant, anti-diabetic, and anti-inflammatory effects are present in isolated components and extract of *B. lupulina*. This in-depth analysis covers the traditional uses, phytochemistry, pharmacological use, and mechanism of action of *B. lupulina*.

Introduction

The utilization of medicinal plants is the subject of countless studies in the search for safe and efficient medical treatments for ailments. Plant-derived medicines have been utilised widely to treat a wide range of illnesses in the traditional medical systems of antiquity, including Ayurveda, Chinese, Egyptian, etc. Particularly secondary metabolites including alkaloids, glycosides, terpenoids, tannins, resins, etc. have been known to have a variety of therapeutic qualities, and plants have long been thought of as the source of chemicals. Research into ethnobotanical applications of the plants led to the discovery of 74% of pharmacologically active plant-derived components. It is estimated that 14-28% of higher plant species are used medicinally (Singh et al., 2016).

An under shrub or herb, *Barleria lupulina* Lindl. (Acanthaceae), is also referred to as kanta vishellakarani or shurma in Bengali (Suba et al., 2002; Shedange and Yadav, 1997), cem mulli or mullukanagaambaram in Tamil (Shedange and Yadav, 1997), landik in Indonesian language (Suba et al., 2002) and in Thailand as slaed pang paw (Suksamrarn, 1986). In English it is been called as hop-headed barleria. The large, well-known, and pantropical genus Barleria contains more than 300 species of herbs and shrubs. Asia and Africa are the primary habitats for *Barleria* species. In India, there are between 26 and 32 species, one subspecies, and one variant *B. prionitis* Linn., *B. noctiflora* Nees., *B. cristata* Linn., *B. montana* Linn., *B. grandiflora* Dalz., *B. lupulina* Lindl., and *B. strigosa* Wild are among the principal medicinal species of the genus Barleria (Balkwill and Balkwill, 1997; Balkwill and Balkwill, 1998; Shedange and Yadav, 1997; Makholela et al., 2003). Recently reviews on this plant have been published (Lekhak et al., 2022; Sawarkar et al., 2022).

Materials and Methods

The relevant literature databases including Science Direct, PubMed, Research Gate, and Google Scholar were searched up to March 31, 2023. The publications were searched for using the keywords "*Barleria lupulina*," "*Barleria lupulina* and Pharmacology," and "*Barleria lupulina* and Phytochemistry". As a result we found articles for each key word. The databases' similar articles were first filtered out. The studies that had nothing

to do with phytochemistry, biological activities, or pharmacology were subsequently eliminated. Patents, abstracts, case studies, and abstracts from congresses and symposiums were removed because they lacked adequate details. Following the exclusion criteria, 44 articles (34 research articles, 6 reference articles, and 4 irrelevant articles) were discovered to be pertinent to *B. lupulina*. Finally, two pieces that discussed its agricultural pursuits were excluded from the inclusion requirements. The phytochemical profile of *B. lupulina* was discovered to be similar to that of *B. prionitis*, thus some articles were added to explain the mechanism and active ingredients behind the pharmacological effects of *B. lupulina*.

Uses in Traditional Medicines

Traditionally, the whole plant or leaf was used in different diseases. They are either administered orally or applied locally. Inhabitants of rural Tamilnadu, India utilized the fresh juice of the crushed *B. lupulina* plant to relieve tension and mental strain (Suba et. al., 2002). Whereas the rural people in West Bengal, India used the plant's aerial portions to treat diabetes, snake bites, and rheumatoid arthritis (Chopra et al., 1968). In case of of snakebites, it was used topically. In addition to snakebites, the Thai people applied topically to treat as an anti-inflammatory against bug bites, herpes simplex, and varicella zoster virus lesions.

The leaves of *B. lupulina* have long been used as a diuretic and tonic as well as a remedy for swelling, indigestion, constipation, jaundice, wounds, scabies, and urinary infections (Kanchanapoom et al., 2001; Lans et al., 2001; Sawangjaroen et al., 2006; Elsai, 1995).

In Thailand, the leaf paste was used as a poultice to treat pain and the leaf juice was given to stop bleeding after a cut. The plant had an anti-acne (Chomnawang et al. 2005) and antiamoebic effect.

Phytochemistry

Phytochemicals like iridoids, iridoid glucosides and glycoside, phenylpropanodanoid glycosides, etc were isolated from the different extracts of the plant. Phytochemicals like barlerin, acetyl barlerin, shanziside and different shanziside derivatives, ipolamiidoside, ipolamiide, saletpangponosides, phlororigodoside, mussaenoside, mussanosidic acid and barlupulins can be classified as iridoid glycosides and iridoid glucosides.

Phytochemicals like, lupulinoside, poliumoside, decaffeoyl acteoside etc. can be included in the category of iridoid di-glycosides. Protocatechonic acid -4-O-β-glucoside, vanillic acid -4-O-β-glucoside, leonuriside may be categorized as phenolic glycosides. Compounds such as forsythoside B, verbascoside (phenyl propanoid glycosides); (+)-lyoniresinol 3α-*O*-glycopyranoside (lignan glycosides); (3R)-1-octan-3yl-β-primeveroside (aliphatic glycoside) and benzyl alcohol β-(2′-O-β-xylopyranosyl) glucopyranoside (benzyl alcohol glycoside) also been reported (Kim et al., 2016). Also, two novel 4,8,8-trimethyl cyclooct-2-enone derivatives chkyunglupulins A and B were isolated. 4-ethyl catechols, 4-methyl catechols and 4-vinyl catechol were tannins isolated from hot aqueous extract from aerial parts of *B. lupulina* (Senger et al., 2016). Thus, *B. lupulina* plant as such can be termed to be containing abundance of glycosidal constituents. However, the natures of aglycones were found to be iridoid, phenylpropanoid and phenolic. The only study conducted on essential oil reported presence of cyclobutane, 1,1-dimethyl-2-octyl, 2-hexyl-1-octanol, 1, 2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester and 1-hentetracontanol as components of essential oil may be termed as terpenoids.

Table I discusses most abundant phytochemicals like iridoid, phenylethanoid glycosides, tannins and components of essential oil of *B. lupulina* along with isolation processes for the phytochemicals and methods used for identifying phytochemicals.

Iridoid glucosides were discovered for the first time in the aerial sections of *B. lupulina* (Suksamrarn et al., 1986). Authors reported about the use of 95% ethanol as a solvent for the extraction. Further, after concentrating the aqueous ethanolic extract and washings with hexane, the lower phase was chromatographed on a silica gel column using methylene chloride, methanol as eluent. Methylene chloride : methanol (90 : 10 and 80 : 20) reported to be containing acetyl barlerin, barlerin and shanzhiside methyl ester. Physical (melting points of acetates) and spectroscopic comparisons UV, IR, ^{1}H and ^{13}C NMR) were compared with reported data to reveal the identities of these compounds. In an effort to correlate the pharmacological properties of the recognized compounds from *B. lupulina*, authors reported the anti HSV-1 activity of compound [**5**] with an IC_{50} value of 41.1 µg/mL. The only other discovered molecule with a C5-hydroxyl group is compound [**5**], indicating that the presence of this group is required for anti-HSV-1 activity (Suksamrarn et al., 2003).

Iridoid compounds [**1**–**10**, **17** and **19**] and four new compounds [**24**–**27**] had no discernible effect on the growth of the stat 3 activated cancer cell lines MDA-MB -231 (breast cancer) and U-251MG (glioblastoma), which are both breast cancer and glioblastoma, respectively. Additionally, scientists discovered that chemicals [**10**] and [**19**] only had weak free radical scavenging action, with an IC_{50} of only 100 g/mL (Kim et al., 2015a).

Two novel compounds (chakyunglupulin A [**29**] and chakyunglupulin B [**30**]), along with six previously found substances, were tested for cytotoxicity and antibacterial activity. None of the compounds were appa-

rently found to be cytotoxic and active against the examined bacteria (Kim et al., 2015b). The presence of cyclobutane, 1,1-dimethyl- 2-octyl, 2-hexyl-1-octanol, 1, 2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester, and 1-hentetracontanol added to the essential oil's antibacterial activity against *Bacillus pumilus* and *Staphylococcus aureus* (Sarmad et al., 2012). Thirteen iridoid glycosides were identified from a 70% ethanolic extract of *B. lupulina*. Using the activity of the enzyme alkaline phosphatase as a marker, the impact of the separated chemicals on the differentiation of the MC3T3-E1 cells was examined. With the exception of compound [5] all substances raised the alkaline phosphatase activity in a dose-dependent manner and at varying intensities Among the compounds tested, ipolamiide [14] showed the strongest stimulatory effect followed by acetyl barlerin [3] and 6-*O*-acetylshanzhiside [23] (Widyowati et al., 2010).

Tables II describes the parent chemical structure and describes some of the chemical constituents isolated from *B. lupulina* relating to the parent structure A respectively. The parent structure A with ^{1}H NMR data are presented. While going through various research papers available relating to the phytochemistry of *B. lupulina,* it was noticed that majority of the compounds isolated from the *B. lupulina* were found to belong to parent structure A category of compounds called as iridoid glucosides. Apart from iridoid glucosides, phenyl ethanoid glycosides are reported to be present in *B. lupulina*. Essential oil as usual was found to be containing various terpenoidal compounds. Terpenoidal compounds such as 1,H-3a methanoazulene, 3,7,-11,15, tetramethyl-2-hexadecanoic acid, benzene, cis-thiosphene, oxyranehexadcyl (phytol), phytol acetate and ethyl 9,12,15-octadecatrienoate were reported in extracts from the leaves of *B. lupulina* (Kumari and Dubey, 2016a). Compounds such as forsythoside B, verbascoside (phenylpropanoid glycosides); (+)-lyoniresinol 3α-*O*-glycopyranoside (lignan glycosides); (3R)-1-octan-3yl-β-primeveroside (aliphatic glycoside) and benzyl alcohol β-(2′-O-β-xylopyranosyl) glucopyranoside (benzyl alcohol glycoside) also been reported (Kim et al., 2016). Flavones 2(4H)-benzofuranone, benzofuranone and phenolics like benzyl benzoate, methyl paraben were also been reported in acetone and methanol extracts of leaves of *B. lupulina* (Kumari and Dubey, 2016b).

Therapeutic Potentials

Antimicrobial activity

Extracts from *B. lupulina* were effective against HSV-2 (Herpes Simplex virus type-2). One of nine iridoid glycosides obtained from the plant's flower extracts that exhibited anti-HSV action was ipolamiidoside [5] (Yoosook et al., 1999; Kanchanapoom et al., 2001; Susksamrarn et al., 2003).

In order to determine the antimicrobial effects of among 19 Thai medicinal plants against acne causing microorganism, *B. lupulina*, along with other three medicinal plants which showed the highest zone of inhibition (Chomnawang et al., 2005).

It was proven from different studies that, *B. lupulina* leaf methanol extract had antibacterial potential and produced zones of inhibition against *B. pumilus*, *S. aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus mutans* and *Salmonella enteritidis* (Doss et al., 2011; Moin et al., 2012; Dey et al., 2014). The plant's fresh extract had a 16.5% concentration of antibacterial activity (Pattanayal et al., 2014).

In a different investigation, it was discovered that the antibacterial properties of acetone, methanol, and water -soluble extracts of B. lupulina's leaf and stem were effective against *S. typhi*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus*. Acetone-soluble leaf and stem extracts induced the largest zone of inhibition for *P. aeruginosa*, and methanol-soluble leaf and stem extracts for *S. typhi*. But *K. pneumoniae* was suppressed by every extract. *B. lupulina* leaves' ethanol and aqueous extracts demonstrated antibacterial effectiveness in a different investigation against *E. coli*, *P. aeruginosa*, *S. aureus*, *S. typhi*, and *K. pneumoniae* (Kumari and Dubey, 2016a, 2016b, and Kumari and Dubey, 2017). *B. pumilis* and *S. aureus* were shown to be effectively inhibited by essential oil from *B. lupulina* leaves. Furthermore, according to Sarmad et al. (2012), the presence of at least 15 components is what gives essential oils their antibacterial properties.

CNS depressant activity

One study examined the effects of a methanol extract of *B. lupulina*'s aerial parts on CNS activity. For this, experimental models involving Swiss albino mice and Wistar rats were used. The methanol extract (100, 200, and 300 mg/kg) lowered the overall behavioral pattern (spontaneous activity, alertness, awareness, pain response, and touch reaction) in a dose-dependent manner. The extract considerably decreased the exploratory behavioral profile (Y-maze test and head dip test) and conditioned avoidance response with each of the tested doses. The methanol extract showed excellent motor incoordination and muscle-relaxing abilities. The extract also prolonged the phenobarbitone sodium-induced sleep time (Suba et al., 2002).

Anti-diabetic activity

The anti-diabetic study was evaluated for methanol extract of aerial portions of *B. lupulina* in streptozotocin-induced male Wistar rats. In comparison to the control group, a methanol extract of the aerial portions of *B. lupulina* significantly reduced blood sugar levels at all levels evaluated 4 hours after administration, and the

effect remained for up to 12 hours. The extract's maximal effect was visible after 12 hours at doses of 200 mg/kg of body weight and higher. The group given 300 mg/kg body weight showed the most significant activity (15.4% blood glucose reduction) after 12 hours after administration, whereas the conventional medication, glibenclamide (10 mg/kg body weight), showed a blood glucose reduction of 18.8% at the same time interval (Suba et al., 2004).

Identification of 4-ethyl catechols, 4-vinyl catechols in hot aqueous extract of an herbal medicine of *B. lupulina* and fermented noni (*Morinda citrofolia*) as cofactors to activate Nrf2, an important pathway to be activated for potential diabetic wound healing activity in a cell line study (Senger and Cao, 2016).

Anti-inflammatory activity

Carrageenan-induced rat paw edema and ethyl phenylpropiolate induced ear edema models were used to assess the *ex vivo* anti-inflammatory properties of methanolic extract of *B. lupulina*. The herb was discovered to have a significant inhibitory effect against edema swelling in live animal models (Wanikiat et al., 2008). Additionally, authors investigated the effect of *B. lupulina* on neutrophil migration and found that it significantly decreased neutrophil chemokinesis and chemotaxis. The plants significantly reduced the release of myeloperoxidase and elastase, according to this study's findings (Wanikiat et al., 2008). Similar to this, *B. lupulina* aerial part methanol extract anti-inflammatory activity had been reported, displaying significant inhibition of carrageenan and serotonin-induced rat paw edema volumes in comparison to the untreated group. Methanol extract significantly decreased granuloma weight in a cotton pellet-induced granuloma model (Suba et al., 2005). Additionally, there are reports about the Nrf2 defense mechanism, which protects against inflammatory damage, was activated by *B. lupulina* hot aqueous extract of aerial parts. Numerous catechols (4-ethyl catechols, 4-methyl catechols, 4-vinyl catechol) identified by LC-MS were found responsible for activating the Nrf2 pathway, were also discovered as a result of this investigation. The results were determined using cell line studies on human dermal microvasular endothelial cells. (Senger et al., 2016). The aqueous fraction of whole plant hydromethanolic extract of *B. prionitis* whole plant have shown significant anti-inflammatory activity in the acute inflammation induced by carageenan, histamine and dextran in rats (Singh et al., 2003). Authors reported the anti inflammatory activity may be due to presence of iridoid glucoside, shanziside methyl ester, acetyl barlerin and barlerin.

Antiarthritic activity

The antiarthritic activity of methanol extract of *B. lupulina* leaves at 300 and 600 mg/kg body weight was examined in models of arthritis produced by formalin, adjuvants, collagen type II, and monosodium iodoacetate using Wistar rats. During the research period, extracts at doses of 300 mg/kg and 600 mg/kg significantly prevented the development of edema and myeloperoxidase activity while significantly restoring antioxidant activity. At 300 mg/kg and 600 mg/kg, methanol extracts significantly increased levels of hemoglobin, serum albumin, total protein, calcium, and phosphorus, while significantly lowering levels of leucocyte count and erythrocyte sedimentation rate were observed (Mazumder et al., 2012).

Anti-osteoporotic activity

Using alkaline phosphatase activity in MC3T3-E1 osteoblast cells as a marker, 32 Indonesian medicinal herbs were examined for their effects on osteoblast development. The 70% ethanol extract of the aerial portions of *B. lupulina* was found to have the strongest alkaline phosphatase-enhancing activity. Utilizing ALP activity as a marker, the effect of the separated chemicals on the differentiation of the MC3T3-E1 cells was examined. With the exception of [**5**], every compound raised the alkaline phosphatase activity, albeit to varying degrees and in a dose-dependent manner. Ipolamiide [**14**], acetyl barlerin [**3**] and 6-O-acetyl-shanziside [**23**], all had the greatest stimulatory effects among the substances examined (Widyowati et al., 2010).

Immunomodulatory activity

According to the findings of an immunomodulatory study conducted on a methanol extract of *B. lupulina* using rats, the immune system was improved by raising blood leukocyte count, spleen weight, spleen leukocyte count, and paw volume on delayed type hypersensitivity footpad thickness (Mazumder et al., 2012).

Anti-cataract activity

The *in vitro* activity was carried out using by glucose-induced caractogenesis using goat lenses. When compared to the positive control group (glucose), the lenses incubated with ethyl acetate fraction of methanol extract of *B. lupulina* at 200 and 400 g/mL concentration seemed to slow the progression of lens opacification and showed a significant restoration of glutathione, superoxide dismutase level and reduced level of TBARS. With a lower IC_{50} value, ethyl acetate fraction of methanol extract demonstrated promising percentage inhibition of aldose reductase activity (Mazumder et al., 2014).

Antiulcer activity

The gastric cytoprotective properties of a methanol extract of the aerial parts of the plant *B. lupulina* were evaluated using a range of ulcer models, such as drug-induced ulcers, constraint ulcers, duodenal ulcers, and pylorus ligated ulcers. The extract at the tested dose of 200 mg/kg considerably reduced the amount of gastric juice, overall acidity, and the ulcer index in pylorus-

Table I

Phytochemicals reported in *Barleria lupulina* along with methodology for isolation and identification

Part	Compound	References	Isolation, identification method
Aerial part	Shanziside methyl ester [1]; 8-*O*-acetyl shanziside methyl ester (barlerin) [2]; 6, 8-*O*-*O*-diacetyl shanziside methhyl ester (acetyl barlerin) [3]	Suksamrarn et al., 1986	Ethanolic extract: Column chromatography; physical comparison and spectroscopic (UV, IR, NMR)
Aerial part	6-*O*-Acetyl shanziside methyl ester [4], ipolamiidoside [5]	Byrne et al., 1987	Column chromatography; ^{1}H and ^{13}C NMR, MS and X-ray diffraction
Aerial part	Shanziside methyl ester [1]; 8-*O*-acetyl shanziside methyl ester (barlerin) [2]; 6, 8-*O*-*O*-diacetyl shanziside methyl ester (acetyl barlerin)[3], 6-*O*-acetyl shanziside methyl ester [4], ipolamiidoside[5], 6-*O*-*p*-methoxy-cis-cinnamoyl 8-o-acetyl shanziside methyl ester [6]; ; 6-*O*-*p*-methoxy-trans-cinnamoyl 8-*O*-acetyl shanziside methyl ester [7]; ; 6-*O*-p-methoxy-cis-coumaroyl 8-O-acetyl shanziside methyl ester [8]; ; 6-*O*-*p*-methoxy-trans-coumaroyl 8-*O*-acetyl shanziside methyl ester [9]	Tuntiwachuwuttikul et al., 1998	Column chromatography followed by re-chromatography and RHPLC;UV, IR, ^{1}H and ^{13}C NMR, HRFAB-MS and comparative study for known compounds
Aerial part	Ipolamiidoside [5], 8-*O*-acetyl-6-*O*-trans-*p*-coumaroyl shanziside [10]; saletpangponoside A [11], saletpangponoside B [12]; saletpangponoside C [13], ipolamiide[14]; phlororigidosideB [15]; 8-*O*-acetyl mussaenoside [16]	Kanchanapoom et al., 2001	Column chromatography followed by HPLC-ODS; ^{1}H and ^{13}C NMR, HRFAB-MS and comparative study for known compounds
Flower	Shanziside methyl ester [1], 8-*O*-acetyl shanziside methyl ester [2], 6, 8-*O*-*O*-diacetyl shanziside methyl ester (acetyl barlerin) [3], 6-*O*-acetyl shanziside methyl ester [4], ipolamiidoside [5], musaenosidic acid [17]; 8-*O*-acetyl shanziside [18], shanziside [19]	Suksamrarn et al., 2003	Column chromatography followed; ^{1}H and ^{13}C NMR, HRFAB-MS and comparative study for known compounds Determination of structure of new compound by 2D-NMR
		Widyowati et al., 2010	Extraction followed by fractionation with polar solvents followed by reversed phase MPLC and pTLC; ^{13}C NMR, HRFAB-MS and comparative study for known compounds

ligated rats. Additionally, it offered crucial protection against ulceration brought on by alcohol, indomethacin, and stress. Additionally, rats given indomethacin had less TBARS (thiobarbituric acid reacting substances) in their stomachs when administered with the extract of the plant. In addition, it offered protection against duodenal ulcers (Suba et al., 2004).

Antiamebic activity

The antiamebic abilities of 12 Thai medicinal herbs were examined against *Entamoeba histolytica* strains HTH-56: MUTM and HM1: IMSS growing *in vitro*. These herbs are frequently utilized by AIDS patients in southern Thailand. The extracts from *B. lupulina*, *Alpinia galanga*, *Boesenbergia pandurata*, *Piper betle*, and *P. chaba*, as well as those from methanol extract *B. pandurata*, were classified as being active, whereas those from *Murraya paniculata* and *Zingiber zerumbet* were classified as being moderately active (Sawangjoroen et al., 2006).

Antioxidant activity

According to reports, shanziside methyl ester and shanziside have a negligible ability to scavenge DPPH (Kim et al., 2015a). The total phenolic content and DPPH free radical scavenging activity of *B. lupulina*'s methanolic leaf and stem extracts were evaluated in a related study. The stem extract was found to have a higher phenolic content, but the leaf extract showed stronger free radical scavenging activity with an IC_{50} value of 48.9 (µg/mL) (Kumari et al., 2017).

Eighty percent (v/v) ethanol at 400 W for 30 sec were shown to be the best conditions for extracting antioxidant compounds by microwave assisted extraction. Four new phenylethanoid glycoside chemicals (lavandulifolioside, cistanoside C, tubuloside B, and betonyoside A) were successfully discovered in the species through analysis using ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (Suhaimy et al., 2021). However, the role of antioxidant in the treatment of different diseases remains to draw any conclusion.

Table I

Phytochemicals reported in *Barleria lupulina* along with methodology for isolation and identification (Cont.)

Part	Compound	References	Isolation, identification method
Essential oil	Cyclobutane,1,1-dimethyl-2-octyl, 2-hexyl-1-octanol, 1, 2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester, 1 -hentetracontanol	Sarmad et al., 2012	GC-MS
Aerial part	Shanziside methyl ester [1]; 8-*O*-acetyl shanziside methyl ester (barlerin) [2]; 6, 8-*O*-*O*-diacetyl shanziside methyl ester (acetyl barlerin) [3], 6-*O*-acetyl shanziside methyl ester [4], ipolamiidoside [5], 6-*O*-*p*-methoxy-cis-cinnamoyl 8-*O*-acetyl shanziside methyl ester [6]; ; 6-*O*-*p*-methoxy-trans-cinnamoyl 8-*O*-acetyl shanziside methyl ester [7]; 6-*O*-*p*-methoxy-cis-coumaroyl 8-*O*-acetyl shanziside methyl ester [8]; 6-*O*-*p*-methoxy-trans-coumaroyl 8-*O*-acetyl shanziside methyl ester [9], 8-*O*-acetyl-6-*O*-trans-*p*-comaroyl shanziside [10], musaenosidic acid [17], shanziside [19]; barlupulin A [24], barlupulin B [25]; barlupulin C [26], barlupulin D [27], lupulinoside [28]	Kim et al., 2015a	Ethyl acetate soluble fraction of aqueous extracts followed by preparative HPLC; LC-MS of extract, ^{1}H and ^{13}C NMR, HRESI-MS, IR and comparative study for known compounds
Aerial part	Chakyunglupulin A [29]; chakyunglupulin B [30]	Kim et al., 2015b	Ethyl acetate soluble fraction of aqueous extracts followed by preparative HPLC; LC-MS of extract, ^{1}H and ^{13}C NMR, HRESI-MS, IR and comparative study for known compounds
Aerial part	Poliumoside [31]; dacaffeoyl acetoside [32], protocatechuic acid 4-O-β-glucoside[33]; vanillic acid 4-*O*-β-glucoside [34], Leonuriside [35], forsythoside B [36], verbascoside [37]	Kim et al., 2016	Ethyl acetate soluble fraction of aqueous extracts followed by preparative HPLC; LC-MS of extract, ^{1}H and ^{13}C NMR, HRESI-MS, IR and comparative study for known compounds
Aerial part	4-Ethyl catechols, 4-methyl catechols, 4-vinyl catechol	Senger et al., 2016	Hot aqueous extract; LC-MS
Leaf	Lavandulifolioside, cistanoside C, tubuloside B, betonyoside A	Suhaimy et al., 2021	Microwave assisted extraction with ethanol (varying concentration); UHPLC-QTOF/MS

Anticlastogenic activity

The chromosome protective ability of aqueous leaf extract of *B. lupulina* was assessed in mice (Sur and Das 131). They split up animals into three groups: pre and post treatment sets I and III respectively. Set II was maintained as control (the mice's whole body was exposed to cobalt (Co-60) 1.2 Gy of γ-irradiation. Set I mice received injections of 1 mL of an aqueous extract per 100 g of body weight, and one hour later, the entire body was subjected to 1.2 Gy of γ-irradiation from cobalt (Co-60). Set III involved the exposure of mice to γ -irradiation (1.2 Gy) from cobalt (Co-60), and following a one-hour injection 1 mL of an aqueous extract per 100 g of body weight. The study of aberration was conducted at 1, 16, 48 hours, 1 and four weeks for every group of animals. There was an increase in aberration in the control (set II) from the initial to 48 hours (16.6%). Similarly, for same for interval, sets I and III had shown aberrations of 7.5% and 4.6%, respectively. Correspondingly. For the set III, the percentage aberration was modest. Comparing set III mice (0.2% with translocation) to set I using chromosomal dissociation, (0.3%) and control set II (1.9 with chromosome dislocation, 1.9% with chromatid beak). The outcomes revealed the aqueous extract of *B. lupulina* played a major part in radiation protection against structural chromosomal damage caused by γ-rays harm in mice.

Antitumor activity

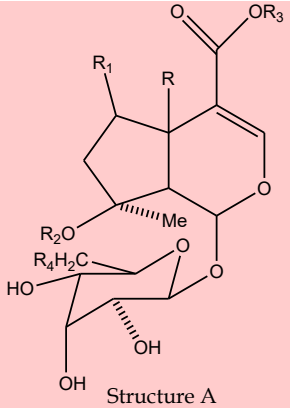
The leaf extract of *B. lupulina* possesses the ability to fully decrease the tumor (ulcer proliferative growth) that was caused by γ-rays (1.2 Gy) that happened near the nostril in fresh water *Oreochromis mossambicus* tilapia fish in nine days (Sur and Dass, 2012).

Structure Activity Relationship

Iridoids belong to the large family of terpene derivatives. Iridoid glycosides are produced from cyclopetanoid monoterpenes with eight, nine, or 10 carbons **(**Boros and Stermitz, 1990). These compounds have a bicyclic cyclopentanoyran ring system, which suggests that the cyclopentane ring serves as the primary ring system in these compounds. Seco iridoids are produced

Table II

Iridoids from *Barleria lupulina*



Structure A

Compound No.	Compounds (Structure A)	R	R1	R2	R3	R4
1	Shanziside methyl ester	H	H	H	Me	OH
2	8-*O*-Acetyl shanziside methyl ester (barlerin)	H	H	Ac	Me	OH
3	6,8-*O*-*O*-Diacetyl shanziside methyl ester (acetyl barlerin)	H	Ac	Ac	Me	OH
4	6-*O*-Acetyl shanziside methyl ester	H	Ac	H	Me	OH
5	Ipolamiidoside	OH	H	Ac	Me	OH
6	6-*O*-*p*-Methoxy cis-cinnamoyl 8-*O*-acetyl shanziside methyl ester	H	*p*-Methoxy cis-cinnamoyl	Ac	Me	OH
7	6-*O*-*p*-Methoxy trans-cinnamoyl 8-*O*-acetyl shanziside methyl ester	H	*p*-Methoxy trans-cinnamoyl	Ac	Me	OH
8	6-*O*-*p*- cis-Coumaroyl 8-*O*-acetyl shanziside methyl ester	H	*p*-cis-Coumaroyl	Ac	Me	OH
9	6-*O*-*p*-Trans-coumaroyl 8-*O*-acetyl shanziside methyl ester	H	*p*-trans-Coumaroyl	Ac	Me	OH
10	8-*O*-Acetyl 6-*O* trans-*p*-coumaroyl shanziside	H	trans-p-Coumaroyl	Ac	H	OH
11	Saletpangponoside A (6-*O*- (4′-*O*-β-glucopyranosyl)-trans-*p*-coumaroyl-8-*O*-acetylshanzhisidemethyl ester)	H	(4‴-*O*-β-Glucopyranosyl)-trans-*p*-coumaroyl-	Ac	H	OH
12	Saletpangponoside B(6-*O*- (4′-*O*-β-glucopyranosyl)-cis-*p*-coumaroyl-8-*O*-acetylshanzhiside methyl ester)	H	(4′-*O*-β-Glucopyranosyl)-cis-*p*-coumaroyl *O*-Glc	Ac	Me	OH
13	Saletpangponoside C (8-*O*-*p*-dihydrocoumaroyl shanzhiside methyl ester)	H	H	trans-p-coumaroyl	Me	OH
14	Ipoliimide	OH	H	H	Me	OH
15	Phlorigidoside B	OH	OH	Ac	Me	OH
16	8-*O*-Acetyl mussaenoside	OH	H	Ac	Me	OH
17	Musaenosidic acid	H	H	H	H	OH
18	8-*O*-Acetyl shanziside	H	H	Ac	H	OH
19	Shanziside	H	H	H	H	OH
20	8-*O*-Acetylipolamiidic acid	OH	H	Ac	H	OH
21	8-*O*-Acetyl-6-*O*-(*p*-methoxy-*cis*-cinnamoyl) shanzhiside	H	*p*-Methoxy-cis-cinnamoyl	Ac	H	OH
22	8-*O*-Acetyl-6-*O*-(*p*-methoxy-*trans*cinnamoyl) shanzhiside	H	p-Methoxy trans-cinnamoyl	Ac	H	OH
23	6-*O*-Acetylshanzhiside	H	Ac	H	Me	OH
24	Barlupulin A	H	OH	Ac	Me	COOH
25	Barlupulin B	H	OAc	Ac	Me	COOH
26	Barlupulin C	H	OH	H	H	COOH
27	Barlupulin D	H	COOH	H	H	OH

Table III

Phytochemicals in *Barleria lupulina* along with pharmacological effect/mechanism of action

References	Phytochemical reported if any	Pharmacological effect/Mechanism of action
Chen et al., 1998	6-O-Trans-p-coumaroyl-8-O-acetyl shanziside methyl ester and its cis isomer	Antiviral- Respiratory syncytial virus
Amoo et al., 2009	Acetyl barlerin, barlerin, shanziside methyl ester, verbascoside, 6-O-acetylshanziside methyl ester	Antifungal- fungi static and fungicidal- Zone of inhibition
Singh et al., 2003	Shanziside methyl ester, barlerin, acetyl barlerin	Acute anti-inflammatory
Ata et al., 2009	Shanziside, 6-O-trans-p-coumaroyl-8-O-acetyl shanziside methyl ester, acetyl barlerin, barlerin	Antioxidant activity- free radical scavenging,
Jaiswal et al., 2010	Acetyl barlerin, barlerin, shanziside methyl ester	Anti-diarrhoeal- Reduction in gastrointestinal motility
Ata et al., 2007, 2009; Amoo et al., 2011	Shanziside, 6-O-trans-p-coumaroyl-8-O-acetyl shanziside methyl ester, acetyl barlerin, barlerin, and 6-O-acetylshanziside methyl ester	Enzyme Inhibitory- AchE inhibition
Suksamrarn et al., 2003	Ipolamiidoside [5]	Anti HSV-1
Sarmad et al., 2012	Cyclobutane,1,1-dimethyl- 2-octyl, 2-Hexyl-1-octanol, 1, 2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester, 1-hentetracontanol	Antimicrobial
Widyowati et al., 2010	8-*O*-Acetylshanzhiside [18], shanzhiside [19], 8-*O*-acetylipolamiidic acid [20], 8-*O*-acetyl-6-*O*-(*p*-methoxy-*cis* cinnamoyl)shanziside [21], and 8-*O*-acetyl-6-*O*-(*p*-methoxy-*trans*cinnamoyl), 6-*O*-acetylshanzhiside [23], also compounds [1-4, 6, 7 and 14]	Anti-osteoporotic (alkaline phosphatase enzyme enhancing)
Senger et al.,2016	4-Ethyl catechols, 4-methyl catechols, 4-vinyl catechol	*In vitro* anti-inflammatory; activation of Nrf2 pathway
Amoo et al., 2009; Zhu et al., 2016; Alipieva et al., 2014	Verbascoside [36]	Fungi static and fungicidal– zones of inhibition Central antifatigue, Neuroprotective, anti-inflammatory, antioxidant,anti-prolifrative, UV-protective against carcinogenic effects
Yang et al., 2020	Forsythoside B [37]	Cardioprotective, anti-inflammatory, neuroprotective, lung protective, antibacterial and anti-tumor

when the cyclopentane ring is broken, while iridoid derivatives are produced when the pyran ring is broken. Many ancient medicinal plants contain iridoids, which are used as bitter tonics, sedatives, antipyretics, cough syrups, wound healers, hypotensives, and remedies for skin ailments. These substances showed hepatoprotective, purgative, hypolipidemic, hypoglycemic, anti-inflammatory, antispasmodic, anti-cancer, antiviral, and antitumor properties (Dinda et al., 2007a). We closely looked the chemical structures of all the iridoids isolated from *B. lupulina* and enlisted them as per the chemical structures A (Table II, Supplementary Figure 1).

B. lupulina crude extracts have antiviral efficacy against HSV-2 (Yoosook et al., 1999). Nine iridoid glycosides were identified from plant's floral extracts, but only one, ipolamiidoside [5], showed anti-HSV action (Suksamrarn et al., 2003). The C5 -OH moiety on the parent structure may be the cause of the anti-HSV action. According to the aforementioned results, positions R1, R2, R3, and R4 may display the pharmacological effects of the phytochemicals and consequently the plant extracts when substituted with various chemical groups.

Shanziside methyl ester [1], 8-*O*-acetyl shanziside methyl ester (barlerin) [2], 6, 8-*O*-*O*-diacetyl shanziside methyl ester (acetyl barlerin) [3]; 6-*O*-acetyl shanziside methyl ester [4], ipolamiidoside [5]; 6-*O*-p-methoxy-cis-cinnamoyl 8-*O*-acetyl shanziside methyl ester [6]; ; 6-*O*-p-methoxy-trans-cinnamoyl-8-*O*-acetyl shanziside methyl ester [7], ipolamiide [14], 8-*O*-acetylshanzhiside [18], shanziside [19], 8-*O*-acetylipolamiidic acid [20], 8-*O*-acetyl-6-*O*-(*p*-methoxy-cis-cinnamoyl) shanziside [21], 8-*O*-acetyl-6-*O*-(p-methoxy-trans-cinnamoyl), shanziside [22] and 6-*O*-acetylshanzhiside [23] were reported alkaline phosphatase stimulatory activity except compound [5] (Widyowati et al., 2010).

Ipolamiide [14] was found to be showing strongest of all the isolated compounds, bears acetyl group at R3,

would be the possible reason for its higher alkaline phosphatase stimulatory effects whereas ipolamiidoside [5] with no such group at R3 remains inactive for this particular therapeutic action. 6,8-*O,O*-diacetylshanzhiside methyl ester (acetyl barlerin, [3]) the next active compound as reported by authors contains two acetyl group (at R2 and R3) and 8-*O*-acetyl shanzhiside [36], having acetyl group at R2 (structure A) would be possibly responsible for lower alkaline phosphatase stimulatory activity than ipolamiide. All other compounds although were found active in stimulating alkaline phosphatase activity contains acetyl group at some other positions. This would be a classical example of understanding SAR among the natural compounds of *B. lupulina* or thereby of other species of genus *Barleria*.

B. prionitis is one of the extensively studied species of the genus *Barleria*, reported to have some identical phytoconstituents with diverse pharmacological actions as to that of *B. lupulina*. Bronchitis and cough are treated with an oral hot water extract of *B. prionitis*' dried leaves and roots (Krishnaraju et al., 2005; Ata et al., 2007). Infants who have RSV are more likely to experience fever and symptoms similar to asthma. A phenolic glycoside called verbascoside and three iridoid glycosides (barlerin, 6-O-trans-*p*-coumatroyl-8-O-acetyl -shanziside methyl ester, and 6-O-cis-*p*-coumatroyl-8-O-acetyl-shanziside methyl ester) were identified from *B. prionitis*. While barlerin was shown to be inactive, researchers reported the antiviral activity of a mixture (1:3) of the substances (6-O-trans-*p*-coumaroyl-8-O-acetyl-shanziside methyl ester and 6-O-cis-*p*-coumaroyl -8-O-acetyl shanziside methyl ester) against RSV (strain A2). Therefore, the coumaroyl moiety may be responsible for the antiviral activity of the compounds (6-O-trans-*p*-coumaroyl-8-O-acetyl-shanziside methyl ester and 6-O-cis-P-coumaroyl-8-O-acetyl shanziside methyl ester) (Dinda et al., 2007b). Because barlerin, 6-O-trans-*p* -coumatroyl-8-O-acetyl-shanziside, and 6-O-cis-*p*-coumaroyl-8-O-acetyl-shanziside methyl ester are also found in *B. lupulina*, it can be concluded that the coumaroyl moiety in structure A played a role in the antiviral effects of the plant.

Cytogenetic Study

Cytogenetic study *on B. lupulina* reveals tetrapoidal nature with chromosome number $2n$ = 40 (Devi and Mathew, 1991).

Toxicology

The acute toxicity study of *B. lupulina* was studied in mice with no adverse effect or mortality. The LD_{50} of methanolic extract was 4.5 g/kg after oral administration and 3.7 g/kg after intraperitoneal administration (Suba et al., 2002).

Conclusion

An extensive literature review identified the isolated compounds and extract of *B. lupulina* as having antibacterial, antiarthritic, CNS depressant, anti-osteoporotic, antioxidant, anti-diabetic, and anti-inflammatory properties.

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Conflict of Interest

Authors declare no conflict of interest

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Author Info
Hemant A. Sawarkar (Principal contact)
e-mail: mrhemant1979@gmail.com