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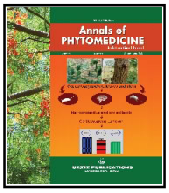

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# Hordenine: Pharmacological, phytochemical, pharmacokinetic and analytical review of the literature

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**Abstract**

We planned to extensively evaluate the phytochemical, pharmacological, pharmacokinetic, and analytical effects of hordenine. Hordenine is a typical tertiary amine, *i.e.*, N-dimethyltryptamine, which is a principal alkaloid of barley (*Hordeum vulgare* L.) and belongs to the family, Poaceae. Synonyms were 4-(2-(dimethylamino) ethyl) phenol, 4-[2-(dimethylamino) ethyl] phenol, and anhaline. The molecular formula is $C_{10}H_{15}NO$. Its chemical structure is the same as stimulants which are in bitter orange. A systematic review of literature search through PubMed, Pubchem, and ScienceDirect electronic databases was conducted for relevant studies reported after 1956 on the effects of hordenine on gastrointestinal disorders, acute lung injury, hyperprolactinemia diabetes, diabetes-related complications, weight loss, and physical fitness, potential roles in skeletal muscle, *Pseudomonas aeruginosa* infections, chronic bacterial infections, antinociceptive, antimicrobial activities, as a sensing inhibitor, beer marker, dopamine D2 receptor agonist, *etc.*, and isolation. A summation of 88 studies was reviewed. There was sturdy evidence for protecting against lipopolysaccharide-induced acute lung injury, analgesic potential, hyperprolactinemia, a significant decrease of DRD2 (dopamine D2 receptor) expression level, FDA's dietary supplement, the potential for controlling nosocomial pathogens, blend of hordenine and insulin (In) outstandingly reduced fasting (f) and postprandial (pp) blood glucose level, a natural product upregulation of *in vitro* translation, serves as a competitive inhibition on signal molecules, Excellent effect on skeletal muscle health by the activation of β, the 2-adrenergic receptor by increasing cAMP signaling acts as an inhibitor of hyperpigmentation. Many studies were conducted on hordenine and have much scope to work on other pharmacological activities like anticancer, hepatoprotective, wound healing, *etc*.

## 1. Introduction

Hordenine is found in mature leaves, bark, and flowers of *Panicum meliaceum* and belongs to the family Poaceae (Ram Rastogi *et al*., 1960). Also seen in algae, cacti, and some species of grass. Other sources of hordenine are *Acacia spirorbis, Ariocarpus scapharostrus, Aspergillus glaucus, Azureocereus ayacuchensis, Boletus zelleri, Cannabis sativa, Cereus jacamaru, Combretum zeyheri, Corphantha bumamma, Corphantha calipensis, Corphantha grenwoodii, Corphantha radians, Corphantha vivipara* (Grundon *et al*., 2007), *Dolchothele surculosa, Mammillaria elongate, Obregonia denegrii, Pelecyphora aselliformis, Desmodium trifolium, Solisia pectinate, Trichocereus pachanoi, Turbinicarpus pseudomacrochele* (Saxton *et al*., 2007).

Hordenine has sources like southern African succulents, *i.e.*, carrion flowers and starfish flowers from the genus of Stapelia. Red marine algae-like *Mastocarpus stellatus*. Hordenine is available in more quantities in many types of cacti, as hallucinogenic properties are peyote (*Lephophora williamsii*), San Pedro cactus (*Trichocereus pachanoi*), and Peruvian torch cactus (*Trichocereus peruvianus*). Hordenine is common in the Amaryllidaceae, *ex*: Crimean snowdrop (*Galanthus plicatus*) and *Eremurus fuscus, Eremurus lutesus* (Cheryll *et al*., 2012). Hordenine is included in many dietary supplements used for athletic performance and weight loss.

Hordenine crystallizes efficiently in colorless prisms and melting points, 117-118°C; b. p.173-174. It sublimes at 140-150°C. It is freely solubilized in $H_2O$, alcohol, ether, and chloroform. It is powerful alkaline and liberates $NH_3$ from its salts (Manske *et al*., 1953). The molecular weight is 165.23. Based on physical and chemical properties and chiefly available in many sources and have much scope to work on many activities. So, decided to do a review priory, to doing research on some activities.

## 2. Materials and Methods

In September 2021, a systematic review was conducted by literature search through PubMed, Pub Chem, and Science Direct electronic databases by using the text word “Hordenine”. All these databases explored titles and abstracts for original research articles in the English language from inception to September 2021.

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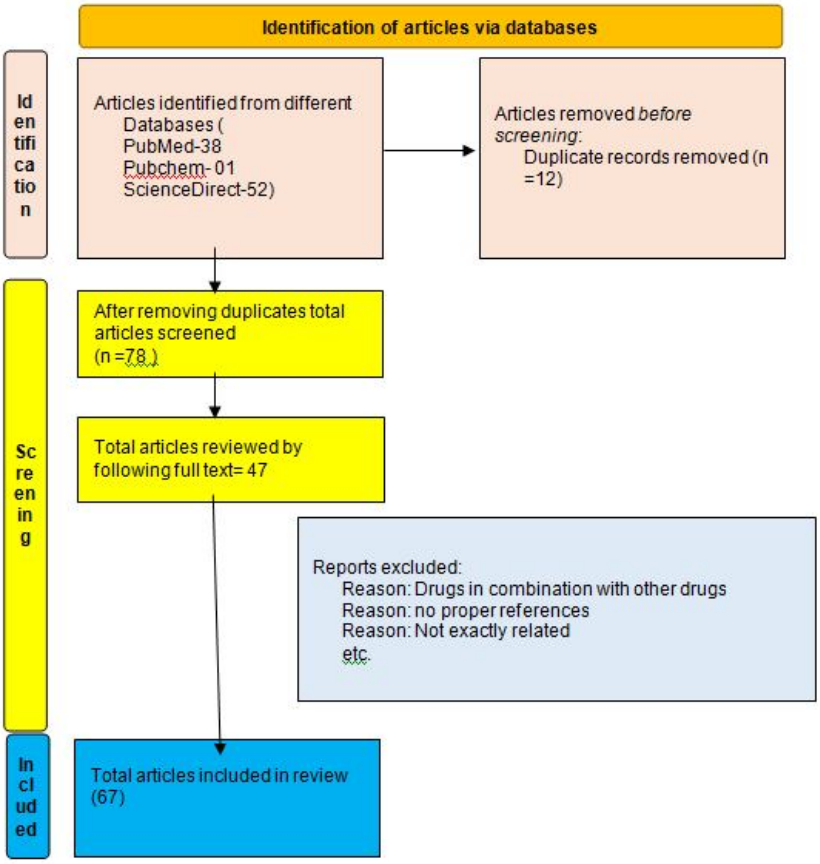


**Figure 1: Prisma statement summarizing identification, screening, eligibility, exclusion, and inclusion aspects of the current study.**

## 3. Results

### 3.1 Pharmacological review

| **Effects of hordenine on lungs** | | |
|---|---|---|
| **Pharmacological activities** | **Compounds involved** | **References** |
| *In vitro* and *in vivo* models of acute lung injury simplified the mechanism and pathways of hordenine to save against LPS-induced acute lung injury (ALI), showing its ability of clinical value. Hordenine efficiently alleviated LPS-induced acute lung injury. The process involves the inhibition of levels of inflammation mediators by suppressing the stimulation of signals like AKT, NF-kB, and, MAPK. | Hordenine dimethyl sulfoxide | Xiyue Zhang *et al.* (2021) |
| The research work reported that *Aconitum tanguticum* shows a strong protecting property against lipopolysaccharide-induced acute lung injury (ALI) in rats by its anti-inflammatory (AI) activity. | Aconitum tanguticum, hordenine | Guotai Wu *et al.* (2014) |
| The inhibition of enzyme studies proved that hordenine inhibits the action of pyruvate dehydrogenase kinase 3 by an $IC_{50}$ value of 5.4 µM. Therefore, hordenine shows an anticancer property on cancerous cells of human lungs (A549 and H1299) with an $IC_{50}$ value. Anyway, it does not stop the cell production of HEK293 by about 200 µm, indicates that it is not harmful to cell lines that are not cancerous. | Hordenine, vincamine, tryptamine, cinchonine, and colcemid. | Saleha Anwar *et al.* (2020) |

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| **Effects of hordenine as a dietary supplement** | | |
| The validation method enables the pharmacokinetic profile of hordenine to determine the high-rise conc. Of hordenine was noticed after 66 ± 15 min, after that reaching a value of 16.4 ± 7.8 µg/l. The overall half-life was 55 ± 18 min. The apparent vol. of distribution will be 6000 ± 2700 l. | Hordenine-rich diet supplements orally | Monika Sobiech *et al.* (2020). |
| The method of LC-MS/MS was applied quantitatively to estimate 5 natural amines and 4 synthetic phenethylamines. The usage of methyl synephrine and isopropyloctopamine are not approved as supplements of diet, hordenine, N-methyltyramine, and octopamine are recently listed on FDA's List. | 5 amines of natural and 4 synthetic phenethylamines | Rahul Pawar *et al.* (2020) |
| A method of validation, *i.e.*, LC high-resolution mass spectrometry quadrupole time-of-flight (LC-QToF-MS) was performed for the synchronous analysis of 112 amine-based components related to ergogenics, anorectics, and many potent compounds include phenethylamines (amphetamines, ephedrine), sibutramine, or yohimbine. The development of like these methods is expected to be regulatory aid to agencies for the detection of unapproved exogenic compounds seen in several products of diet. | 27 weight loss and as an ergogenic diet supplements | Bharathi *et al.* (2019) |
| The quantitatively estimating method NMR was developed and used as a concurrent estimation of the concentrations of the phenethylamines. The work showed that an excellent instrument to screen and identify phenethylamines is NMR in diet products. | Eight phenethylamines. phenethylamine, synephrine, oxilofrine, hordenine, *etc.*, Quercetin, hordenine, vanillin | |
| The study is to find out the capability of *Calligonum azel* maire as a part of the food. The HPLC-DAD monitoring proved that the methanol extract does not have a biologically potent compound with unfavorable activities, so quercetin, hordenine, and vanillin were more in the flowers, leaves, and roots. Results conclude that the suitability of *Calligonum azel* maire as traditional food. | Quercetin, hordenine, and vanillin | Marwa Bannour *et al.* (2016) |
| The method was validated on 45 supplements of diet. Caffeine, p-synephrine, and ephedrine were seen to be there as a restorative in more than 50% of the samples from the market as capsules or bulk forms of it. | Caffeine, p-synephrine, hordenine, octopamine, tyramine, ephedrine, and salicin | Carine Viana *et al.* (2015) |
| Functional foods are the same that of conventional food is used as part of a daily diet, and are shown to have physiological benefits, decreasing the risk of chronic diseases more than basic nutritional functions. | Neutraceuticals | Pushpangadan *et al.* (2014) |
| A group of 3 dietary supplements referring to substances that contain bitter orange has been prepared, and the concentrations of 5 different alkaloids and caffeine were estimated by using many methods of analysis. | Synephrine, octopamine, tyramine, N-methyltyramine, hordenin, total alkaloids, and caffeine | Sander *et al.* (2008) |
| A method called liquid chromatographic atmospheric-pressure ionization electrospray mass spectrometry (LC-API-ES-MS) has been used for the determination of 5 bitter orange alkaloids. This method allows for the estimation of the superior alkaloid synephrineand any few alkaloids in different types of supplement diets. | Synephrine, octopamine, n-methyltyramine, tyramine, and hordenine | Karsten Putzbach *et al.* (2007) |
| Adrenergic amines seen in *Citrus aurantium* extracts invoke analytic useful chemiluminescence with acidic potassium permanganate with polyphosphates. This method of identification rapidly determines the synephrine in using column chromatography of monolithic. | Synephrine, octopamine, tyramine, and hordenine | Teo Slezak *et al.* (2007) |
| **Effects of hordenine as DRD2 (dopamine D2 receptor)** | | |
| They were a notable decrease in dopamine D2 receptor expression level, an extraordinary increase in PRL prolactin secretion, and an improvement of cAMP-response element-binding protein expression in MMQ cells in the total barley Maiya alkaloids + group with haloperidol. | Total barley Maiya alkaloids group, hordenine group, total barley Maiya alkaloids + group with haloperidol, total barley Maiya alkaloids + group with forskolin, total barley Maiya | Xiaoyun Gong *et al.* (2021) |

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| | alkaloids + group with 8-bromo-cAMP, hordenine + haloperidol group, hordenine + group with forskolin, and hordenine (H) + group with 8-bromo-cAMP | |
| The hordenine levels observed in plasma seem to be very less to evoke a straight reaction with the D2 dopamine receptor often relates to food benefit, but there is a chance of double effect with alcohol or N-methyl tyramine. | Hordenine | Thomas Sommer *et al.* (2020) |
| The current work introduced a detection method virtually to detect food constituents, those that may modify dopamine D2 receptor signaling. On the basis of its occurrence in beer, we recommend hordenine remarkably promotes the elevation of mood from beer. | 13,000 different compounds | Thomas Sommer *et al.* (2017) |
| **Effects of hordenine on prolactin** | | |
| They were a notable decrease in dopamine D2 receptor expression level, an extraordinary increase in PRL prolactin secretion, and an improvement of cAMP-response element-binding protein expression in MMQ cells in the total barley Maiya alkaloids + group with haloperidol. | Total barley Maiya alkaloids group, hordenine group, total barley Maiya alkaloids + group with haloperidol, total barley Maiya alkaloids + group with forskolin, total barley Maiya alkaloids + group with 8-bromo-cAMP, hordenine + haloperidol group, hordenine + group with forskolin, and hordenine + group with 8-bromo-cAMP | Xiaoyun Gong *et al.* (2021) |
| The hordenine treatment re-establish estradiol, promotes the incre -ased growth of the pituitary gland, and decreases the prolactin gathering in the blood serum and pituitary gland of rats by restric-ting the MAPK (p38, ERK1/2, and JNK) stimulation and prepar-ation of cytokine's of inflammation, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). The effect of antiprolactinoma hordenine was regulated by suppressing the signaling pathway activation of MAPK in rats. | *Hordenine* from *Fructus* hordei, Germinatus | *Xiong Wang et al.* (2020) |
| **Effects of hordenine on diabetes** | | |
| The work was focused to prepare a product with millets suitable for the usage of diabetic patients. Selected millets, *viz*., foxtail millet, proso millet, kodo millet, and barnyard millet were collected from the near shops. Wheat flour (*Triticum aestivum* L.), green-gram dhal (*Phaseolus aureus* Roxb), oats, soybean (*Glycine max* Merr), barley, fenugreek seeds, and gums were arranged from a grocery shop. | Carbohydrates, minerals, and fats | Mounika *et al.* (2021) |
| The combination of hordenine and insulin (I) effectively decreased pre-prandial and post-prandial glucose levels of blood in mice with diabetes. The mechanism behind this additive effect of hordenine and insulin (I) has to be identified. | Hordenine and Insulin | Shuhao Su *et al.* (2018) |
| **Effects of hordenine on pigmetation** | | |
| Results show that the hordenine inhibited the process of formation of melanin by controlling cAMP preparation, that is intricated in the expressed proteins of formation of melanin, and recommends that hordenine is an excellent suppressor of high pigmentation. | Hordenine | Sang-Cheol Kim *et al.* (2013) |
| **Effects of hordenine on nociceptive activity** | | |
| Results show that the hordenine inhibited the process of formation of melanin by controlling cAMP preparation, that is intricated in the expressed proteins of formation of melanin, and recommends that hordenine is an excellent suppressor of high pigmentation. | Hordenine | Sang-Cheol Kim *et al.* (2013) |

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| **Effects of hordenine on nociceptive activity** | | |
| Current work was performed for the isolation of phytoconstituents to assess the antinociceptive activity of the hydroethanolic fraction produced from the leaves of *P. aculeata* methanolic extract. *P. aculeata* is not only used as a portion of food from plants with good nutritious properties and also has pain-killing properties. It is the earliest biological activity that is proved for this plant species. | Tryptamine, abrine, mescaline, hordenine, petunidin, di-tert -butyl-phenol isomers, and quercetin | Nícolas de *et al.*, (2015) |
| **Effects of hordenine on antibacterial activity** | | |
| The result of developing a host-pathogen system of tomato *S. marcescens* as a prototype to find out the activity of hordenine on quorum sensing (QS)-mediated pathogen activity under a suitable environment. Hordenine can be a good pesticide or pesticide accelerant to treat crop diseases. | Hordenin at 25, 50 and 100 µg/ml | Jin-Wei Zhou *et al.* (2019) |
| Hordenine can be used as a competitive suppressor for signaling molecules and also behave as a new QS-based drug to protect from infections of foodborne. | Hordenine with netilmicin | Jin-Wei Zhou *et al.* (2018) |
| The complete report of the study recommends the additive antibiofilm activity of anisotropic hordenine-fabricated gold nanoparticles and hordenine for treating chronic infections of bacteria caused by biofilms forming pathogens. | Anisotropic hordenine-fabricated gold nano-particles) and hordenine | Rajkumari *et al.* (2017) |
| The process of modeling the interactions of structure between human hormones and AHL-receptors LasR of *Pseudomonas aeruginosa* and TraR of *Agrobacterium tumefaciens* confirms that the competitive binding capacity of the sex hormones of humans. The study proves the strong interactions between the hormonal communications of bacteria and eukaryotes. | Hordenine and human sexual hormone estrone | Amelie Beury-Cirou *et al.* (2013) |
| **Effects of hordenine on the gastrointestinal tract** | | |
| In the plant cell walls of wheat, barley, and oats, β-glucan is present in the cell walls of baker's yeast, many funguses, and some micro -organisms. The prominent useful properties of β-glucan include its use for the preventing also treatment of digestive diseases. | Beta-glucans | Nupur Mehrotra *et al.* (2021) |
| The 3 phenethylamine AR regulators that are N-methyltyramine, synephrine, and hordenine in CRP, AFI, and AF were isolated. That was seen that N-methyltyramine can relax smooth muscles of the small intestine and control intestinal propulsions of mice. The N-methyltyramine effect on relaxation of intestinal smooth muscle can be suppressed by a-methyl-l-tyrosine. | 30 formulas of 3 Citrus species | Jianan Ni *et al.* (2019) |
| The serotonin receptor 4b which is a 5-HTR4b assay could be used to test pharmacy multiple libraries to detect new remedies for IBS-C. This study proves that antimicrobials react to the microbiota of the gut and also with the host as humans. | Hordenine (antibiofilm) | Emily *et al.* (2019) |
| The study carried out a similarity search to detect regions same in sequence as T-cell activation of gluten peptides in the accessible gluten sequences: The hordenine in barley, secalin in the rye, and avenins in oats. The detected peptides were identified as T-cell activation properties. | Gluten, secalin, hordeine | Willemijn Vader *et al.* (2003) |
| **Effects of hordenine on ANS** | | |
| The present study checked for N-methylated tyramine derived and their glucosylated forms in Citrus plant species, along with octopamine and synephrine, also coming from tyramine, upright the mechanism of particular biosynthetic pathways of adrenergic compounds designed to act on biotic stress. | Hordenine-glucoside | Luigi Servillo *et al.* (2017) |
| In the current study after taking feed with hordenine is observed in the horse's blood or urine, In such cases, horse racing may be the fact of using illegal substances. Pharmacological model reports prove that hordenine is an inversely acting adrenergic drug. It allows producing norepinephrine from stores. | Hordenine | Hapke *et al.* (1995) |

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| **Effects of hordenine on muscles** | | |
| The work provides proof that several factors present in food may affect skeletal muscle by improving the cAMP signal activating of β2-AR. | Osthole, gramine, and hordenine | Miho Chikazawa *et al.* (2018) |
| **Effects of hordenine on liver** | | |
| Investigation of the alkaloids from *Senecio scandens* shows that a novel natural product is compound 6, from the genus, Senecio was obtained for the earliest time are compounds 3, 4, and this plant was obtained for the first time are compounds 2, 5. Compound 1 shows a potential growth suppressing effect on hepatocytes at 100 µmol x L(-1). | Adonifoline, 7-angeloylturneforcidine, hordenine, 1, 3, 6, 6-tetramethyl-5, 6, 7, 8-tetrahydro-isoquinolin-8-one(TTI), 4-(pyrrolidin-2-one) -phenyl acetic acid(PPAA), (4-pyrrolidinophenyl) acetic acid(PAA) | Daopeng Tan *et al.* (2010) |

## 3.2 Phytochemical review

| **Phytochemical activities** | **Compounds involved** | **References** |
|---|---|---|
| The present research on different species of cactoideae and peireskioideae both with their full chemical profile which relates to effects genetically and environmental, biological potentials, and well being can be a good presentation to the welfare health of humans and preserve the biodiversity. | Carbohydrates, nitrogen compounds, polyphenols terpenoids. mucilage, phenethylamines, flavonol glycosides, betalains, triterpenoids. | Tania da Silveira *et al.* (2020) |
| The work result shows producing gramine and hordenine from the leaves and roots, respectively, in their 19th barley strains. In a further way, in the new barley cultivator called Barke, the great amount of hordenine in roots and the scarcity of gramine refers to allowing biosynthesis. Gramine cannot be seen in the root extracts. | Two alkaloids gramine and hordenine | Mauro Maver *et al.* (2020) |
| The application of the protocol is to demonstrate the preparation of more than 50 important N-methylamines which include more particular reductive N-methylations molecules of life science and regular drugs, those are hordenine, venlafaxine, imipramine, and amitriptyline. | 50 N-methylamines | Kishore Natte *et al.* (2017) |
| Investigation of phytoconstituents of the *polyalthia longifolia* var. *pendula* leaves ethanolic extract has made to separate 7 diterpenoids of clerodane and 5 alkaloids. | 7 diterpenoids, 5 alkaloids. | Koneni Sashidhara *et al.* (2009) |
| 4 alkaloids that are phenethylamine derived have been separated from the fraction of n-butanol of *Stapelia hirsuta* L. in all parts except roots. | N-acetyl hordenine, hordenine, candicine, hordenine-1-O-beta-D-glucoside, luteolin-7-O-beta -D-glucopyranoside | Marwan Shabana *et al.* (2006) |
| Galanthindole a novel alkaloid with an indole group, was separated from *Galanthus plicatus* ssp. *byzantinus* (Amaryllidaceae), Joining a non-fused indole ring, galanthindole can be shown as a model of the earliest subgroup of the Amaryllidaceae alkaloids. 2 other bases, (+)-11-hydroxyvittatine and hordenine, are also isolated. | Hydroxyvittatine and hordenine | Nehir Unver *et al.* (2003) |
| 10 alkaloids isolated from extracts of *Mexican cactus*, *Dolichothele uberiformis* (Zucc.) Br. and R. Spectral data support and identified another new alkaloid (uberine) as 5-methoxy-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. | (--)-synephrine, (--)-longimammine, N-methyl-3,4-dimethoxy-beta-phenethylamine, N-methyl--4-methoxy-beta-phenethylamine, (--y-normacromerine, N-methyltryramine, hordenine, longimammatine | Ranieri *et al.* (1977) |

### 3.3 Pharmacokinetic review

| Pharmacological activities | Compounds involved | References |
|---|---|---|
| This work on the *in vitro* blood-brain barrier permeability profile of the standardized GBE was estimated by the parallel artificial membrane permeability study. In the current method, rapid LC-ESI-MS is selected for observing the content of tyramine, N-methyltyramine, hordenine, and also the products of *Ginkgo biloba*. | Tyramine, N-methyltyramine, hordenine | Arpad Konczol *et al.* (2016) |

### 3.4 Analytical review

| Analytical activities | Compounds involved | References |
|---|---|---|
| The report of the analysis of food supplements that are adulterated was examined by the Authority of Netherlands Food and Consumer Product Safety during the period October 2013 and 2018. | Over all 417 products were tested in which 264 (64%) contain one or more pharmacologically potent constituents or toxins of plant, *i.e.*, caffeine, synephrine, sildenafil, icariin, sibutramine, higenamine, hordenin, phenethylamine, methyl synephrine, DMAA, phenolphthalein, octopamine, and ephedrine | Jacqueline *et al.* (2019) |
| The quantitative method which is NMR was introduced for the concurrent estimation of the different conc.s of the phenethylamines. The work shows that a strong instrument to screen and identify phenethylamines is NMR or any substances in supplements of diet. | Eight phenethylamines phenethylamine, synephrine, oxilofrine, hordenine, β-methylphenethylamine, N-methyltyramine, octopamine and deterenol | Jianping Zhao *et al.* (2018) |
| Reports on drinking demonstrated that consumption of beer causes detection of hordenine conc.s in serum and found a linear excretion of hordenine correlating to alcohol blood concentration, proves that hordenine can also be utilized as a good marker for beer consumption qualitatively and quantitatively. | Hordenine-D | Irina Steiner *et al.* (2016) |
| Projecting the utilization of analyzing directly in real-time ionization coupled with high-resolution time-of-flight mass spectrometry in reporting the substitution of *Sceletium tortuosum* marketed products. It is a strong tool not only to detect drugs of the plant source of abuse, for psychotropic alkaloids but can also report the occurrence of prohibited substances and their contaminants. | Hordenine, ephedrine. | Ashton Lesiak *et al.* (2016) |
| In the present study, a new sorbent was fabricated for selective solid-phase extraction of hordenine in biological samples. The recoveries were from 91.5 to 93.6% and from 88.4 to 92.7% for the samples of spiked plasma and urine, respectively, with the relative standard deviations being <4.8%. | Hordenine | Yong Gang Chen *et al.* (2015) |
| The current study is a sensitive and selective UPLC-MS/MS method to estimate the N-methylcytosine in rat plasma emerged. When hordenine was added as an internal standard, protein precipitation by acetonitrile-methanol (9:1, v/v) was utilized to make samples. The absolute bioavailability of methylcytosineine was found to be 54.6%. | N-methylcytosine, hordenine | Shuang Wang *et al.* (2015) |
| The samples of 100 were estimated by gas chromatography-mass spectrometry using a computer-based search and strong hits were verified for creditability. Few toxic and biological effects of those drugs came out. | 4-methyl cathinone(4-MC), flephedrone, trifluoromethyl phenyl-piperazine, methylone. butylone, hordenine, and harmane). | Frank Musshoff *et al.* (2013) |
| Collection of 8 sports drug samples from distinct contest sites was done, which shows to have similar urine specimens as designated by steroid profile analysis and proved by DNA-STR analysis. | Hordenine and serpine-Z4 | Mario Thevis *et al.* (2012) |
| In the current study, compounds like galanthamine, lycorine, homolycorine, tazettine, haemanthamine, narciclasine, and tyramine like 70 alkaloids were found by GC/MS in 25 *Galanthus* | Hordenine and its derivatives | Strahil Berkov *et al.* (2011) |

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| elwesii and 7 *Galanthus nivalis* species. The sample reports of years and transplanting experiments show the determination of genetics of synthesis of alkaloids in the 2 varieties of Galanthus studied. | | |
| Most of the adrenergic protoalkaloid are seen in fruit and the peel of *Citrus aurantium* is synephrine (S). The work developed a positive-ion mode liquid chromatography/tandem mass spectrometry (LC/MS/MS) method for the estimation of the major (synephrine (S) and minor (tyramine, N-methyltyramine, octopamine (O), and hordenine quantitatively. | Synephrine, tyramine, N-methyl tyramine, octopamine, and hordenine | Bryant Nelson *et al.* (2007) |
| In the current work, the rapid separation of phenethylamine alkaloids was done by the chromatographic performance of a *Penta fluoro* phenyl propyl stationary phase was evaluated. The method developed will be compatible with the checking of the quality of Citrus plant material and marketed products. | (+/-)-octopamine, (+/-)-synephrine, tyramine, N-methyltyramine, and hordenine | Federica Pellati *et al.* (2007) |
| In this work to analyze alkaloids in hardinggrass (*Phalaris aquatica* L.) an excellent (HPTLC) method was used. Reports show considerable differences in the constituents of alkaloids within harding grass populations. | Methyltyramine, hordenine, gramine, and 5-methoxydi methyltryptamine | Lili Zhou *et al.* (2006) |
| In this work, a novel piperidyl alkaloid, haloxynine was separated from the aerial parts of *Haloxylon salicornicum*, which is a plant that has many alkaloids and is characterized based on mass spectrometry, 1H, and 13C NMR. A Gas LC/MS analysis report shows the occurrence of 16 alkaloids. | Piperidine, halosaline, anabasine, hordenine, N-methyltyramine, haloxine, and aldotripiperideine. | El-Shazly *et al.* (2005) |
| The leaves of *Phalaris aquatica* L contain 2 types of toxic substances, indole alkaloids, primarily dimethyltryptamines, and N-methyl tyramines. An acceptable correlation was seen between toxin levels by ELISA and determined a most laborious TLC method. In the Phalaris breeding program, the method has been incorporated. | Hordenine, tyramine, tyrosine | Skerritt *et al.* (2000) |
| 43 strains of barley which include ancestral, landraces, Middle Eastern lines, and new cultivators will grow in two different types of environments. Production of hordenine in barley roots was estimated at the one-leaf stage by the HPLC method and, in 2 strains for about 35 days. Hordenine produced was approxi-mately 8 times high in plants that were grown under low light intensity. | Hordenine | Lovett *et al.* (1994) |
| In this study, the method was developed for the preparation of extracts and to check the quantity of hordenine and gramine from barley tissue using HPLC analysis. Quantification was done by taking peak area, and the relationship between peak area and concentration of authentic standards was linear for both hordenine and also gramine. Good variations in the capability of 3 strains of barley to make hordenine and gramine were identified. | Hordenine and gramine | Hoult *et al.* (1993) |
| In this work, the production of alkaloids from barley was estimated by the HPLC method. Hordenine was produced from the barley roots in a hydroponic system for about 61 days. The quantity reached a maximum, of 2 µg/plant/day, at 35 days, and then decreased. The proof of the effects of organoleptic and primary barley allelochemicals at the ranges produced by plants proves that the phytoconstituents of barley have potential activity in a crop field. | Hordenine, gramine | Liu *et al.* (1993) |
| In this immunological study, hordenine cross-reacted with different ELISA or RIA kits were used for the testing of samples of urine. Morphine-ELISA kit was more sensitive, and etorphine-and buprenorphine-ELISA kits were less sensitive to hordenine cross-reactivity. | Hordenine, oxymorphone, hydromorphone, and apomorphine | Singh *et al.* (1992) |

## 4. Discussion

A systematic review by literature search through PubMed, Pubchem, and Sciencedirect electronic databases was conducted for relevant studies reported after 1956 on the effects of hordenine use on gastrointestinal disorders, acute lung injury, hyperprolactinemia, diabetes, and diabetes-related complications, weight loss, and physical fitness, potential roles in skeletal muscle, *Pseudomonas aeruginosa* infections, chronic bacterial infections, antinociceptive, antimicrobial activities, as a quorum sensing inhibitor, beer marker, dopamine D2 receptor agonist, *etc.*, and isolation.

A total of 88 studies were viewed. There was strong evidence for protecting against LPS-induced acute lung injuryinvolves the inhibition of inflammatory mediator levels by suppressing stimulation of AKT, NF-κB, and MAPK signals, people use hordenine orally for fatness, enhances athletic performance, and is presently listed in the Advisory List of FDA's Dietary supplement as an ingredient, the analgesic potential also proved.

Hordenine has shown a significant decrease in DRD2 (dopamine D2 receptor) shows a decrease in dopamine D2 receptor-expressing levels, a significant increase in PRL prolactin secretion, and an improvementin cAMP/PKA/CREB levels.

Hordenine acts as a good dietary supplement in the form of capsules, health drinks, or health drinks. Roasted seeds of the safflower, mixed with chickpeas, barley, or wheat, are used as a snack food in Ethiopia and Sudan (Sunil Gomashe *et al.*, 2021). The effect of antiprolactinoma of hordenine was conducted by suppressing the MAPK signaling pathway in rats, the hordenine treatment re-establish estradiol, and promotes the increased growth of the pituitary gland.

The combination of hordenine and insulin prominently reduces pre-prandial and post-prandial blood sugar levels in mice with diabetes. Hordenine decreased the melanogenesis process by inhibiting cAMP production, which involves the expression of proteins melanogenesis-related and suggests hordenine is a good suppressor of hyperpigmentation.

Hordenine has shown antinociceptive activity. Hordenine is effective as a strong pesticide or pesticide accelerator in the treatment of infections of crops and can behave as a new QS-based agent on pathogens of food and hordenine as biofilms forming is used for treating chronic bacterial infections.

In gastrointestinal disorders, it has been investigated as N-methyltyramine can acts as a smooth muscle relaxant in the small intestine of mouse and stop spropulsions of the small intestine. The property of N-methyltyramine as smooth muscle relaxation in the small intestine will be suppressed by a methyl-l-tyrosine. Hordenine on biological models shows that is an inversely acting adrenergic drug. It acts by liberating norepinephrine.

Hordenine constituents may enhance cAMP signaling by the activation of α2-AR and show an effect on skeletal muscle and prove a prominent growth inhibitory effect against hepatocytes. Drinking, studies demonstrated that consumption of beer leads to traceable concentrations of hordenine in the serum and observed a linear elimination of total hordenine by correlating to alcohol concentration in blood, which expresses hordenine used as a marker for beer consumption both qualitatively and quantitatively.

Studies introduced a method that is positive-ion mode liquid chromatography/tandem mass spectrometry (LC/MS/MS) to determine quantitatively the major synephrine and minor tyramine, N-methyltyramine, octopamine, and hordenine adrenergic protoalkaloids.

Determination of hordenine production in roots of barley was at the one-leaf stage analysis by HPLC and in 2 species for about 36 days. Production of hordenine was about 7 times more in plants that grow under lower light.The barley pharmacologically active phytoconstituents lead to a prominent action as defensive in crop fields.

## 5. Conclusion

The observed or reported improvements in phytochemical, pharmacological, pharmacokinetic, and analytical studies were conducted on hordenine like diabetes-related complications along with insulin, weight loss and physical fitness, potential roles in skeletal muscle, *Pseudomonas aeruginosa* infections, chronic bacterial infections, antinociceptive, antimicrobial activities, as a quorum sensing inhibitor, beer marker, dopamine D2 receptor agonist.

Hordenine is an inversely acting adrenergic drug, that treats digestive diseases, improves hormonal communications, and suppressor of high pigmentation, concluded that hordenine can be used alone or in combination with other compounds to show its effects in different formulations and has much scope to work on many other activities like anticancer, hepatoprotective, wound healing, *etc.*, as it is a potential alkaloid.

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## Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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