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Review

Therapeutic Effectiveness of Hernandezine in Medicine for the Treatment of Cancer and other Human Complications: A Biologically active Bisbenzylisoquinoline Alkaloid from Nature

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Abstract

Alkaloids are widely distributed in nature, especially in plants, animals, microorganisms and marine organisms. Hernandezine is a biologically active bisbenzylisoquinoline class alkaloid found to be present in different species of Thalictrum. The present review describes the biological potential and therapeutic effectiveness of hernandezine in medicine for the treatment of human disorders and associated secondary complications. The aim of the present paper is to collect all the scientific data of hernandezine from different scientific databases, including Scopus, Science Direct, Google, PubMed and Google Scholar and analyzed in the present paper in order to know the therapeutic potential of hernandezine in medicine. Present paper mainly focus on the pharmacological activities of hernandezine, however, pharmacokinetic data of hernandezine has also been described in the present review. Present review scientific data revealed the biological significance of hernandezine in medicine for the treatment of human disorders and associated secondary complications. Present review scientific data describe the medicinal importance of hernandezine through its therapeutic effectiveness on pancreatic cancer, hepatocellular carcinoma, type 2 diabetes, melanoma, colon cancer, glioma cells, acetylcholine receptor, hair cells, Ca^{2+} release, multidrug-resistance, permeabilization and TNF-α production. However, immunosuppressive potential and pharmacokinetic parameters of hernandezine were also described in the present work in order to know the different molecular mechanism of hernandezine. Present review also described the different molecular mechanisms of hernandezine. However, detailed preclinical and clinical scientific investigation is utmost important in the scientific fields in order to claim its therapeutic application in human disorders and associated secondary complications.

Keywords: Hernandezine, medicine, pancreatic cancer, hepatocellular carcinoma, type 2 diabetes, melanoma, colon cancer, glioma, acetylcholine receptor, hair cells, Ca^{2+} release, multidrug-resistance, immunosuppressive effect, pharmacokinetic

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Plant derived herbal products have an important role in the human healthy lifestyle due to their vast therapeutic potential in medicine against different kinds of human disorders and complications. Herbs and their derived byproducts, including pure phytochemicals have been utilized as medicines and drug lead molecules in the healthcare system for the development of better drugs against human disorders and complications. The World Health Organization (WHO) also recognized the importance of herbal products in medicine throughout the world. Pure phytochemicals such as as-

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pirin, reserpine, and digitalis are the best examples of plant derived phytochemicals used in medicine for different medicinal purpose.[1–7] Phytochemicals are derived from different types of medicinal plants and have been used as drugs and Nutraceuticals in medicine. Alkaloids, terpenoids, glycosides, and flavonoids class of phytochemicals are mainly responsible for the pharmacological activities of herbal products and their derived drug molecules and also utilized in healthcare system for different medicinal purpose.[8–10] Natural products constitute a unique source of phytocompounds with high scaffold diversity and vast therapeutic potential in medicine. Natural phytoproducts could be a valuable lead for small molecular drug design and discovery and more than 80% of drug substances are natural products which are a rich source of bioactive compounds with high structural diversity.[11–13] Plants-derived bioactive compounds are useful to the human being for the preparation of food material and drugs in the modern age and nature is the source of all the raw materials that we need for different medicinal purpose in medicine.[14–16] Traditional and complementary medicine is a substantial health resource for preventing and managing the health conditions of aging populations. Herbal medicine has a huge market predicted to increase to $200 billion per year by 2025.[17] Plants, as a rich source of bioactive compounds, and have been utilized medicinally for millennia. The low cost, high accessibility, and proven effects make herbal medicine extensively used worldwide especially in Asia.[18] Plant based food, such as cereal, vegetables and herbs as well as their processed products, contains a diverse range of bioactive constituents, including dietary fibers, vitamins, minerals, carotenoids, and polyphenols that are beneficial to human health. Sufficient intake of plant based food not only sustain life, but also reduce the risk of diseases, such as cardiovascular diseases and cancer.[19] Herbal medicines are defined by the World Health Organization as remedies containing "herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients of plants, or other plant materials, or combinations.[20] Chinese herbal medicine has been used in China for thousands of years to maintain health and treat disease. Practitioners of Traditional Chinese medicine (TCM) have accumulated a wealth of knowledge regarding herbal therapeutic effects based on clinical observations. Kampo medicines and traditional Chinese medicines, which have long been used to treat human disease.[21–23] TCM has been used in China and other Asian countries for the treatment of human disorders. Several herbs used in TCM have also been used in Western medicine. TCM was one of the commonly available mode of healthcare throughout eastern Asia before the modern Western medicine. TCM are multi ingredient extracts with low adverse effects which have been used for the treatment of human complications.[24–28]

An overview of Alkaloids

Alkaloids have been reported as one of the important groups of phytoconstituents obtained from natural sources.[29] Medicinal plants containing alkaloids are also used as folk medicines.[30] Alkaloids are naturally occurring organic compounds contain nitrogen atoms and could be categorized into pyridine, indole, tropane, aporphine, purine, quinoline, isoquinoline, phenanthrene, pyrrolizidine, phenylethylamine, imidazole, indolizidine, piperidine, and pyrrolidine alkaloids (Fig. 1).[31,32] There are many known types of alkaloids, about 10,000 of them. So far, nearly 100 alkaloid compounds have been used or used in clinical trials.[33] Naturally occurring alkaloids are produced in living organisms, such as plant species, fungi, animals and microorganisms, via secondary metabolic pathways.[34] A wide range of food products obtained from vegetable and botanical sources, such as seeds, cereals (millet, sorghum, buckwheat, maize), pollen and honeys, processed cereal-based foods, teas, herbs, and food supplements contain numerous class of alkaloidal compounds.[35] Notably, alkaloids have attracted tremendous attention in modern medicine due to their wide clinical application.[36] Plant extracts rich in alkaloid content have been utilized in medicine for treating and controlling dementia for a long time.[37] Alkaloids also serve as a defense mechanism for plants or fungi and gained recognition for their valuable medicinal and pharmacological properties.[38] Alkaloids are secondary metabolites which have anti-cancer, anti-diabetic and anti-inflammatory potential in medicine.[39] Plant alkaloids possess numerous medicinal properties such as oxidative stress modulation, inhibitor of the production of pro-inflammatory cytokines, suppressor of pro-inflammatory mediators, elevator of the levels of an anti-inflammatory cytokines and suppressor of p38 MAPK pathway.[40]

Hernandezine

Hernandezine (Fig. 2) is a biologically active bisbenzylisoquinoline alkaloid found to be present in *Thalictrum hernandezii, Thalictrum fendleri, Thalictrum podocarpum, Thalictrum rochebrunianum, Thalictrum glandulosissimum* and other species of Thalictrum. Hernandezine had been clinically used for the treatment of hypertension, protected hair cells from aminoglycoside-induced damage, inhibiting protein kinase C signaling events in human peripheral blood T cells and neuronal nicotinic acetylcholine receptors (nAChRs), and blocking non-voltage-operated Ca^{2+} entry activated by intracellular Ca^{2+} store depletion induced by thapsigargin in rat glioma C6 cells and in human leukemic HL-60 cells. Hernandezine putatively induced cytotoxicity against a repertoire of cancer cell lines involving energy and autophagy-related gene 7 (Atg 7)-dependent autophagy. Hernandezine selectively in-

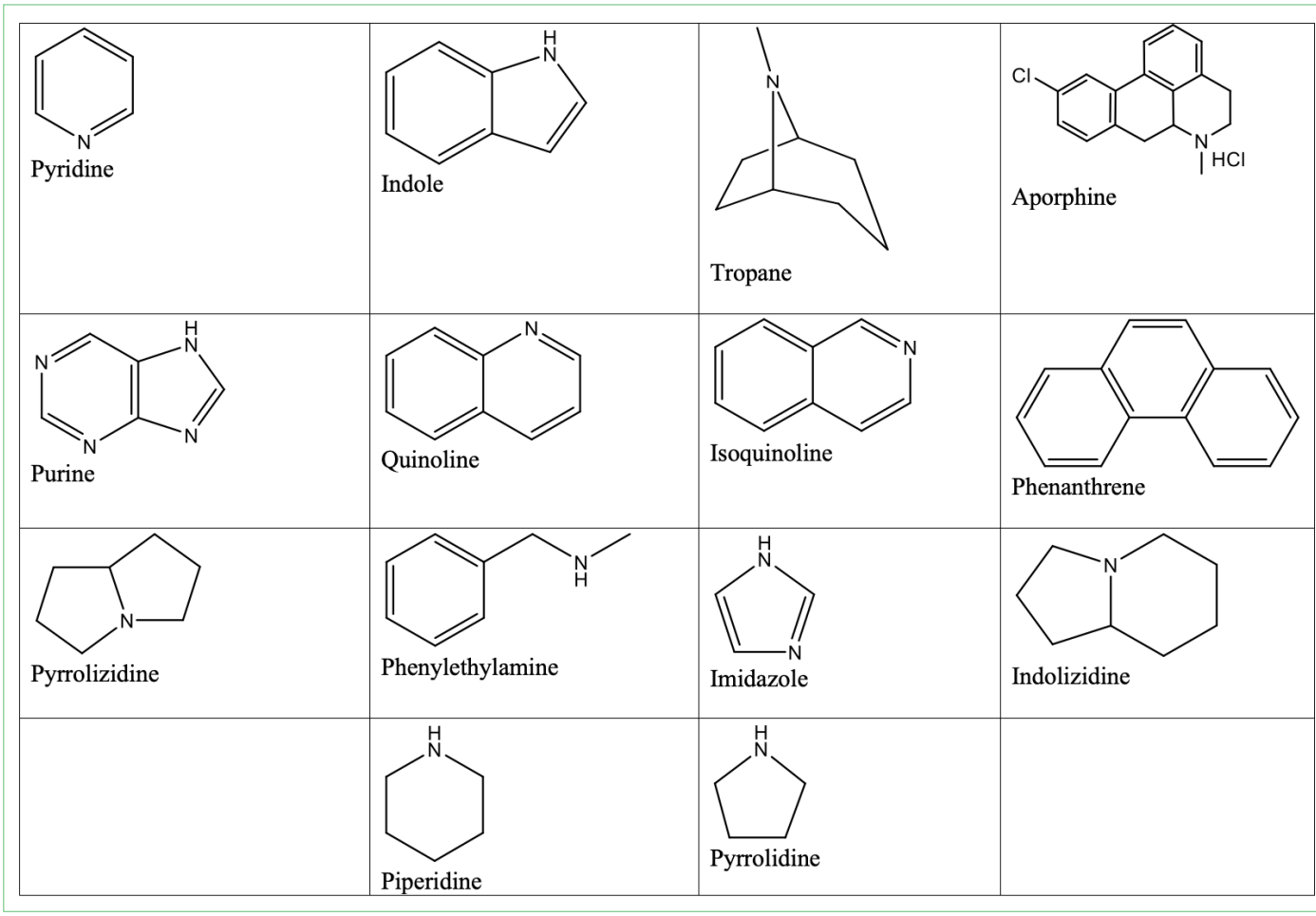

Figure 1. Chemical structure of alkaloid class.

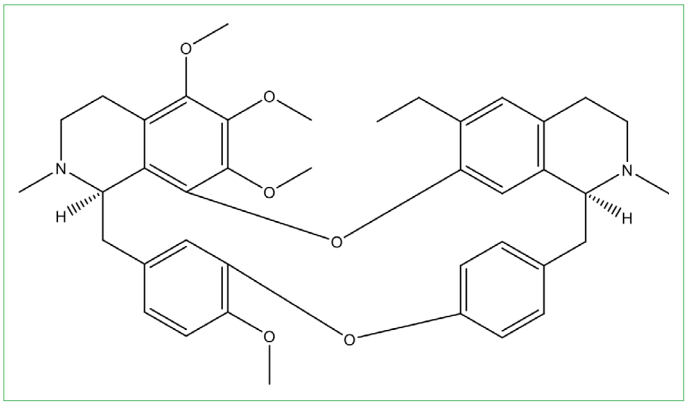

Figure 2. Chemical structure of Hernandezine.

hibited the function of ABCB1 relative to MDR-linked ABC drug transporters ABCC1 and ABCG2.[41] Hernandezine extracted from *Thalictrum simplex* has inhibited of protein kinase C signaling in human peripheral blood T cells and repression of lipopolysaccharide (LPS) induced tumor necrosis factor-α (TNF-α) generation in human macrophage cells. Hernandezine was most effective alkaloid to cause autophagy and autophagic cell death in apoptosis resistant cells via activating AMP activated protein kinase (AMPK) pathway directly.[42] Hernandezine isolated from *Thalictrum flavum* raises the resistance reversal factor for doxorubicin and vincristine to 34 and 356 fold in resistant KB-V-1 cells in comparison to wild KB-3-1 cells and 46 and 435 fold for doxorubicin and vincristine respectively in resistant ABCB1 overexpressing variant NCI-ADRRES cells in comparison to wild ovarian carcinoma cell line OVCAR-8 cells. Hernandezine is known as a Ca^{2+} channel antagonist and an inducer of autophagic cell death in drug-resistant cancers possibly via direct activation of AMPK.[43–45] Hernandezine has long been used for treating hypertension and angina pectoris. Hernandezine blocks the influx of calcium via non selective cation channels in HL-60 cells.[46] Hernandezine isolated from *Thalictrum glandulosissimum* and found to have antitumor, antiplatelet aggregation and calcium channel blocking potential. Hernandezine is an adenosine monophosphate-activated protein kinase (AMPK) agonist that induces apoptosis and autophagy and promotes tumor cell death.[32] Hernandezine selectively inhibited the function of ABCB1 relative to MDR-linked ABC drug transporters ABCC1 and ABCG2. Hernan-

dezine significantly enhanced drug-induced apoptosis and reversed ABCB1-mediated multidrug resistance in cancer cells at nanomolar concentrations.[47,48] Hernandezine was found to possess antimicrobial activity against *Mycobacterium smegmatis* at concentrations of 100 microgram/ml.[49]

Pharmacological Activities of Hernandezine

Pancreatic Cancer

Biological role of autophagy in hernandezine-induced cell death in human pancreatic cancer cell lines have been investigated. Hernandezine dose-dependently suppressed cell proliferation, promoted autophagy and induced autophagic death in pancreatic ductal adenocarcinoma (PDAC) cell lines Capan-1 and SW1990. Hernandezine (1-40 μM) promoted the conversion of LC3-I to LC3-II, and hernandezine exerted concentration-dependent and time-dependent effects on autophagy activation in PDAC cells. Further, autophagic vacuoles were significantly increased in hernandezine-treated cells. Moreover, hernandezine activated autophagy by increasing the phosphorylation of AMPK and decreasing the phosphorylation of mTOR/p70S6K. Furthermore, hernandezine concentration-dependently enhanced reactive oxygen species (ROS) generation in PDAC cells which signified its therapeutic potential for the treatment of pancreatic cancer.[32]

Hepatocellular Carcinoma

Biological potential of hernandezine from *Thalictrum simplex* for their antitumor effects has been investigated in hepatocellular carcinoma (HCC) in HepG2 and Hep3B cells along with their molecular mechanisms. Hernandezine significantly induced G0/G1 phase arrest, inhibited the proliferation and promoted cell apoptosis in liver cancer cell lines. The antitumor effects of hernandezine on liver cancer cells were mediated by phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT) pathway and ROS. After hernandezine treatment, ROS accumulated in liver cancer cells and caused mitochondria injury which further influenced the expression of apoptosis-related proteins and eventually resulted to HepG2 and Hep3B cell apoptosis. Hernandezine showed a tumor restrain function in HepG2 and Hep3B bearing nude mice, which signified its promising antitumor potential for the treatment of HCC.[42]

Melanoma

Biological potential of hernandezine in melanoma have been investigated and found to inhibit proliferation and induce apoptosis in melanoma A375 cells and B16 cells. In hernandezine-treated melanoma cells, G0/G1 cycle arrest occurred accompanied by significantly downregulated levels of phosphorylated JAK2 and STAT3. Hernandezine-treated melanoma cells exhibited autophagy-specific structures, autophagy markers (LC3II/LC3-I), and autophagic flow over time. Hernandezine could induce autophagy via the AMPK-mTOR pathway, thereby inducing apoptosis.[50]

Colon Cancer

Biological potential of the total alkaloids of *Thalictrum glandulosissimum* and hernandezine were analyzed and found to be effective for treatment of mice bearing P388 leukemia, S180 ascites and C26 colon cancer. Hernandezine inhibited the growth of mouse L1210 cells and human oral cancer KB cells *in vitro* markedly, but its inhibitory effect on normal hemopoietic progenitor cells (CFU-GM) in mice was relatively low. Hernandezine blocked cell-cycle transfer from G1 to S phase, and its cytocidal action could be cell cycle specific which further signified its potential on colon cancer.[51]

Glioma Cells

Biological effects of hernandezine, a structural analogue of tetrandrine, on Ca^{2+} mobilization were studied in rat glioma C6 cells. Hernandezine alone did not affect the resting cytoplasmic Ca^{2+} concentration but inhibited the peak and sustained elevation of cytoplasmic Ca^{2+} induced by bombesin and thapsigargin. Hernandezine did not increase inositol 1,4,5-trisphosphate accumulation by themselves but inhibited inositol 1,4,5-trisphosphate accumulation elevated by bombesin. Hernandezine inhibited Ca^{2+} release from intracellular stores as well as Ca^{2+} entry from extracellular medium evoked by bombesin. In addition, hernandezine also inhibited inositol 1,4,5-trisphosphate accumulation induced by bombesin in rat glioma C6 cells.[52]

Type 2 Diabetes

Biological potential of hernandezine from Thalictrum in activating AMP-activated protein kinase (AMPK) and treating T2 diabetes in mouse models has been investigated in various cells and tissues, including primary hepatocytes, skeletal myotubes cell lines, as well as major metabolic tissues from diabetic (db/db) and diet-induced obesity (DIO) model mice. Hernandezine prevented pAMPK from dephosphorylation to prolong its activity, disproving previous direct activation model and providing a new model to explain hernandezine-mediated AMPK activation. Long-term oral hernandezine treatment potently reduced body weight and blood glucose in both type 2 diabetes mullitus (T2DM) mouse models by increasing glucose disposal and reducing lipogenesis. Hernandezine indirectly activates AMPK by suppressing its dephosphorylation. Oral hernandezine effectively alleviated hyperglycemia and reduced body weight in T2D mouse models and could be a potential therapeutic agent for T2DM.[45]

Acetylcholine Receptor

Biological effects of bis-benzylisoquinoline alkaloids on two of the major neuronal nicotinic acetylcholine receptors (nAChRs), the alpha3-containing nAChR (alpha3*nAChR) endogenously expressed in PC12 cells and the rat alpha7-nAChR heterologously expressed in GH4C1 cells has been investigated using patch-clamp technique. Hernandezine reversibly inhibited both receptors. The results demonstrate that hernandezine and other alkaloids are nAChRs antagonists but hernandezine displaying selectivity for one of the major neuronal subtype, the alpha7 nAChR. The different potencies and multiple modes of action on nAChRs may help to better understand the pharmacology of these receptors and to aid in novel drug design.[53]

Immunosuppressive Effect

Biological potential of tetrandrine and its analogues for their immunosuppressive effect on human peripheral blood T cells has been investigated. Tetrandrine inhibited phorbol 12-myristate 13-acetate (PMA) + ionomycin-induced T cell proliferation, interleukin-2 secretion and the expression of the T cell activation antigen, CD71. Moreover, hernandezine was the most potent inhibitor of protein kinase C signaling events among all the tetrandrine analogues studied and could also induce cellular apoptosis which is defective in autoimmune diseases.[54]

Hair Cells

Hair cell damage can result from aging, genetic mutations, excess noise exposure, and certain medications including aminoglycoside antibiotics. A library of 502 natural compounds has been screened in order to identify novel hair cell protectants using the larval zebrafish lateral line and identified four bisbenzylisoquinoline derivatives, including hernandezine which robustly protected hair cells from aminoglycoside-induced damage. Further, the natural compounds confer protection by reducing antibiotic uptake into hair cells and showed that hair cells remain functional during and after incubation in bisbenzylisoquinoline derivatives. Further, these natural compounds represent a novel source of possible otoprotective drugs that may offer therapeutic options for patients receiving aminoglycoside treatment.[55]

Ca^{2+} Release

Biological effects of tetrandrine and its closely related analogues, hernandezine and berbamine on Ca^{2+} entry and Ca^{2+} release were compared in fura-2-loaded HL-60 cells. Berbamine was much less potent than tetrandrine and hernandezine in inhibiting Ca^{2+} entry activated by thapsigargin. Furthermore, berbamine was much less effective than tetrandrine and hernandezine in suppressing TSG-induced Mn^{2+} entry. Berbamine was also less effective than both tetrandrine and hernandezine in causing Ca^{2+} release from internal stores.[56] Biological effect of tetrandrine and hernandezine to SK&F 96365 in fura-2-loaded endothelial cells from human umbilical vein and bovine pulmonary artery has been investigated. SK&F 96365 as well as tetrandrine and hernandezine antagonized depletion-induced Ca^{2+} entry. The results suggest that these putative inhibitors interact with Ca^{2+} entry triggered by depletion of the internal Ca^{2+} stores.[57] Tetrandrine and thapsigargin mobilized the same Ca^{2+} pool and tetrandrine-induced intracellular Ca^{2+} release was independent of protein kinase C activity and ox-adrenoceptor activation and tetrandrine blocked the voltage-insensitive Ca^{2+} entry pathway activated by thapsigargin. These dual effects on HL-60 cells were also observed with hernandezine, a thapsigargin-like compound and in another cell type, murine B lymphoma M12.4 cells.[58]

Multidrug-Resistance

Biological potential of a wide range of diversity and relatively nontoxic nature of natural products for a potential modulator of ABCB1 have been investigated. Hernandezine was identified as a potent and selective reversing agent for ABCB1-mediated multidrug resistance (MDR) in cancer cells. Hernandezine is selective for ABCB1, effectively inhibited the transport function of ABCB1, and enhances drug-induced apoptosis in cancer cells. Hernandezine significantly resensitizes ABCB1-overexpressing cancer cells to multiple chemotherapeutic drugs at nontoxic, nanomolar concentrations. Hernandezine has great potential to be further developed into a novel reversal agent for combination therapy in MDR cancer patients.[47] Drug resistance hinders most cancer chemotherapies and leads to disease recurrence and poor survival of patients. Hernandezine, putatively induce cytotoxicity against a repertoire of cancer cell lines (HeLa, A549, MCF-7, PC3, HepG2, Hep3B and H1299). Hernandezine possess the highest efficacy in provoking such cell death when compared with other compounds and confirmed that isoquinoline alkaloid is structurally varied from the existing direct AMP activated protein kinase (AMPK) activators.[46]

Permeabilization

Biological potential of tetrandrine and its close analogues on spontaneous Ni^{2+} entry (leak) in fura-2-loaded HL-60 cells has been investigated and was found to be strongly inhibited by tetrandrine. Further, a comparative study of the effects of tetrandrine and its very close analogues, hernandezine reveals that the methoxyl group at the R2 position of tetrandrine appears to be crucial in enhancing *Quillaja saponaria*-promoted Ni2+ entry in HL-60 cells.[59]

TNF-α Production

Biological potential of hernandezine on TNFα production has been investigated and found that hernandezine inhibited LPS-induced TNFα expression/production in human macrophage cells (THP-1 and U937 lines). Activation of AMPK is required for hernandezine-induced anti-LPS response. Hernandezine was unable to further inhibit LPS-mediated TNFα production in caAMPKα-expressing cells. Hernandezine inhibited LPS-induced ROS production and nuclear factor kappa B (NFκB) activation. Treatment of hernandezine in *ex-vivo* cultured primary human peripheral blood mononuclear cells also largely attenuated LPS-induced TNFα production. Further, AMPK activation by hernandezine inhibits LPS-induced TNFα production in macrophages/monocytes.[60]

Pharmacokinetics

Biological interaction of hernandezine and doxorubicin on pharmacokinetics has been investigated on male Sparague-Dawley rats. Plasma concentrations of hernandezine and doxorubicin were determined by the LC-MS/MS method and found that there were significant differences in the Cmax and AUC0-∞ of doxorubicin in the single drug group and combined drug group, indicating that hernandezine could improve the absorption of doxorubicin. However, doxorubicin in combination, in turn, reduced the free drug concentration of hernandezine, possibly because doxorubicin enhanced the hernandezine drug-protein binding effect.[48] A simple, specific and sensitive liquid chromatography tandem mass spectrometry (LC-MS/MS) method has been developed and validated for the quantification of hernandezine in rat plasma and tissues after intravenous administration. The chromatographic separation was achieved by using an Agilent ZORBAX Eclipse Plus C18 column. Calibration curves were linear over the ranges of 20.0-4000ng/ml for both plasma samples and tissue samples (r>0.991). The developed method was successfully applied in the pharmacokinetics and tissue distribution study of hernandezine after intravenous administration.[41]

Conclusion

In the present review we have described the biological importance of alkaloidal class phytochemical hernandezine in medicine. Present work described the biological potential of hernandezine in medicine for the treatment of human disorders and associated secondary complications with their underline molecular mechanism. The aim of the present review paper is to collect the scientific data of hernandezine from various scientific databases, including Scopus, Science Direct, Google, PubMed and Google Scholar and analyzed in the present work in order to know the therapeutic potential of hernandezine in medicine. However, pharmacokinetic parameters of hernandezine were also described in the present review in order to know the clinical aspects of hernandezine in medicine. All the scientific data of hernandezine have been collected from research article, review paper, and book chapters through different scientific databases in the present review work. Present review scientific data revealed the biological significance of hernandezine in medicine which was found to be present in the different medicinal plants (Table 1). Present review scientific data describe the medicinal importance of hernandezine in medicine due to its therapeutic effectiveness on pancreatic cancer, hepatocellular carcinoma, type 2 diabetes, melanoma, colon cancer, glioma cells, acetylcholine receptor, hair cells, Ca^{2+} release, multidrug-resistance, permeabilization and TNF-α production (Fig. 3). However, immunosuppressive effect and pharmacokinetic parameters of hernandezine were also discussed in the present review in order to know its therapeutic potential in medicine. Further, scientific data analysis of hernandezine in the present paper also described that different molecular mechanisms (Table 2, Fig. 4) were responsible for the pharmacological activities of hernandezine. However, detailed preclinical and clinical scientific

Table 1. Natural occurrence of hernandezine

S. No.	Biological Source	Reference
1.	*Mycobacterium smegmatis*	[49]
2.	*Thalictrum fendleri*	[41]
3.	*Thalictrum glandulosissimum*	[32,51]
4.	*Thalictrum hernandezii*	[41]
5.	*Thalictrum podocarpum*	[41]
6.	*Thalictrum rochebrunianum*	[41]
7.	*Thalictrum simplex*	[42]

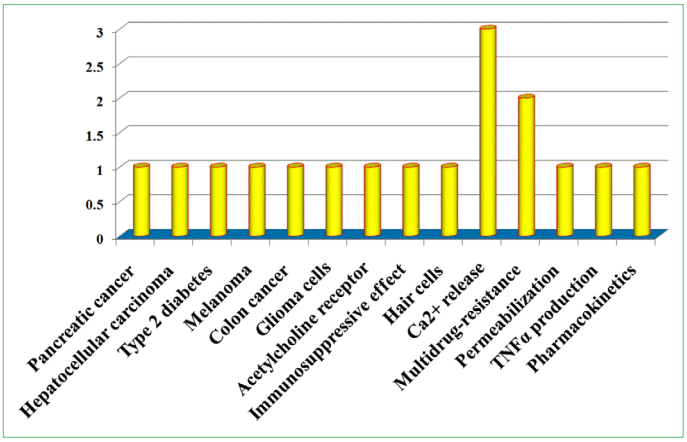

Figure 3. Biological Potential of Hernandezine in human disorders.

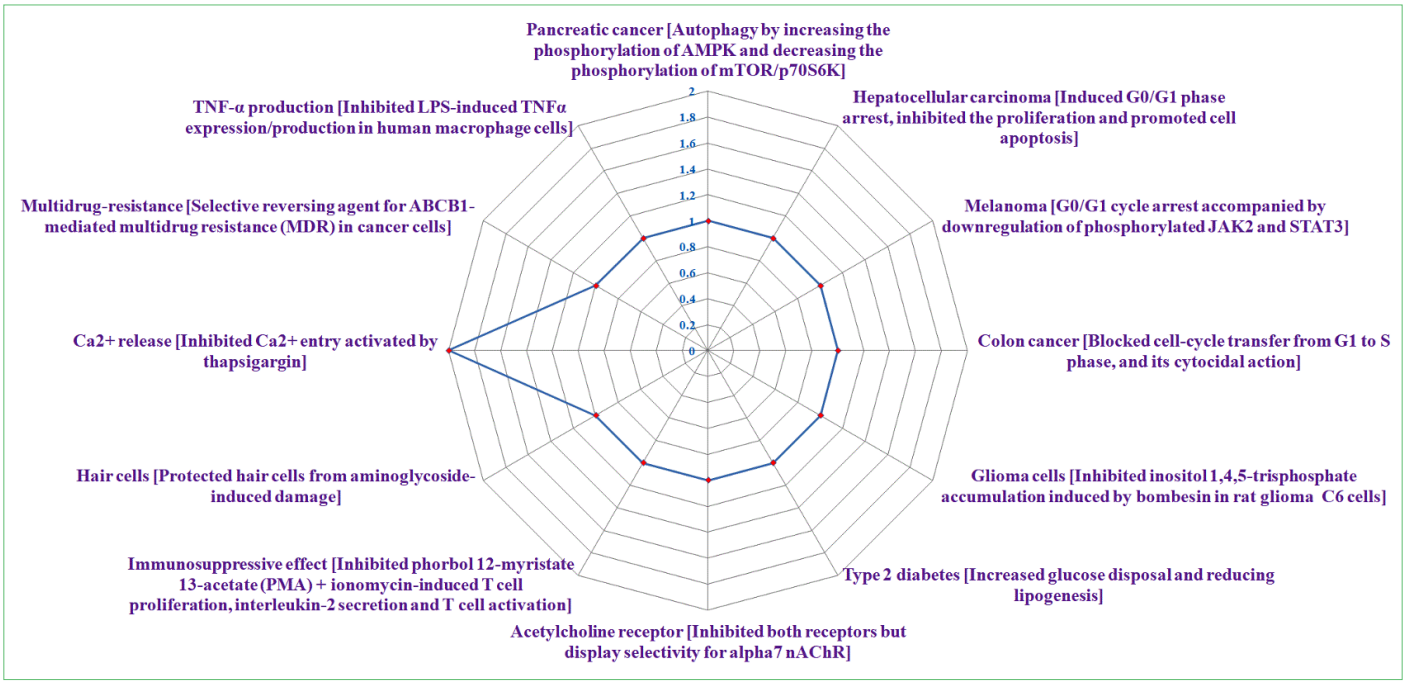

Figure 4. Molecular mechanism of hernandezine in medicine.

Table 2. Molecular mechanism of hernandezine

S. No.	Pharmacological activity	Molecular Mechanism	Reference
1.	Pancreatic cancer	Hernandezine activated autophagy by increasing the phosphorylation of AMPK and decreasing the phosphorylation of mTOR/p70S6K.	[32]
2.	Hepatocellular carcinoma	Hernandezine significantly induced G0/G1 phase arrest, inhibited the proliferation and promoted cell apoptosis in liver cancer cell lines.	[42]
3.	Melanoma	G0/G1 cycle arrest accompanied by significantly downregulated levels of phosphorylated JAK2 and STAT3.	[50]
4.	Colon cancer	Hernandezine blocked cell-cycle transfer from G1 to S phase, and its cytocidal action.	[51]
5.	Glioma cells	Hernandezine inhibited inositol 1,4,5-trisphosphate accumulation induced by bombesin in rat glioma C6 cells.	[52]
6.	Type 2 diabetes	Hernandezine treatment potently reduced body weight and blood glucose in both type 2 diabetes mullitus (T2DM) mouse by increasing glucose disposal and reducing lipogenesis.	[45]
7.	Acetylcholine receptor	Hernandezine reversibly inhibited both receptors but display selectivity for one of the major neuronal subtype, the alpha7 nAChR.	[53]
8.	Immunosuppressive effect	Tetrandrine inhibited phorbol 12-myristate 13-acetate (PMA) + ionomycin-induced T cell proliferation, interleukin-2 secretion and the expression of the T cell activation.	[54]
9.	Hair cells	Hernandezine robustly protected hair cells from aminoglycoside-induced damage.	[55]
10.	Ca2+ release	Hernandezine inhibiting Ca2+ entry activated by thapsigargin. Hernandezine antagonized depletion-induced Ca2+ entry.	[56,57]
11.	Multidrug-resistance	Hernandezine was identified as a potent and selective reversing agent for ABCB1-mediated multidrug resistance (MDR) in cancer cells.	[47]
12.	TNF-α production	Hernandezine inhibited LPS-induced TNFα expression/production in human macrophage cells.	[60]

investigation is utmost important in the scientific fields in order to claim its therapeutic application in human disorders. Present review scientific information of hernandezine will be beneficial for all the scientific peoples to investigate the health beneficial aspects of hernandezine in medicine.

Disclosures

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