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Review article

Medicinal importance, pharmacological activities, and analytical aspects of hispidulin: A concise report

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ABSTRACT

Herbal medicines have been played an important role in the human civilization since very ancient time as a food, cloth, medicine and other aspects. Some of the important drugs in the modern medicine were derived from the natural sources such as aspirin, digitalis, quinine, vincristine, vinblastine etc. Hispidulin (4′, 5, 7-trihydroxy-6-methoxyflavone) is a flavones derivative found in plant such as *Grindelia argentina*, *Arrabidaea chica, Saussurea involucrate, Crossostephium chinense,* Artemisia and Salvia species. Hispidulin have antioxidant, antifungal, anti-inflammatory, antimutagenic, and antineoplastic properties. So far, various analytical methods have been investigated and developed for detection of hispidulin in the plant materials. Productions of hispidulin through different tissue culture techniques have been also investigated. Present review summarized medicinal uses, pharmacological activities and analytical aspects of hispidulin. From the above mentioned aspects, we can conclude that, this review will be helpful to the researcher in the field of natural product for the development of novel molecule for the treatment of different disorders.

1. Introduction

Herbs play an important role in the human civilization as they have been used for different purpose in different field such as medicine, nutraceuticals, perfumery, beverages, fragrances, cosmetics and dyeing industry. From the ancients times herbs were mainly used for the treatments of various disorders until the synthetic drugs developed in the world. More than 40% of prescription drugs in the world were mainly derived from herbal source. Herbs, vegetables and fruits contain numerous phytochemicals such as phenolic compounds, nitrogen compounds, carotenoids, ascorbic acid etc.[1] Different color, flavor and smell of plants were mainly due to the presence of different phytoconstituent present in the plants. They play an important role in the plant's defense mechanism against various diseases.[2] For the search of better therapeutic goal, plants are still considered as one of the important sources of materials. More than 50% of the prescribed drugs in the Europe and USA are derived from natural sources such as plants or their derivatives.[3] Many of these plants products and their crude extracts were used in different types of traditional medicine. Medicinal plants play a key role in health care as more than 80% of the world's populations relying on the traditional medicine for their primary health care. In spite of tremendous development in the field of allopathy, medicinal plants and their derived products are still used in the modern medicine throughout the world. In India more than 7300 plant species are used in traditional health care systems for the treatment of different disorders. The most important chemical constituents of plants are alkaloids, tannin, flavonoid and phenolic compounds etc. In recent years, treatment of infectious disease using antimicrobial drugs has developed multiple drug resistance.[4] Medicinal herbs have been used as remedy for the treatment of pain throughout history including some of most important analgesic prototypes i.e. salicylic acid and morphine was originally derived from plant sources. Natural products are believed to be an important source of new chemical substances for the developments of Nobel medicine for the treatment of various disorders.[5] Plants play a dominant role in the maintenance of human health since ancient times till today. According to World Health Organization (WHO), medicinal plants would be the best source to get a variety

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of drugs. Plants develop different bioactive molecules, making them a rich source of different types of medicinal compound. About 80% of individuals from developed countries use traditional medicine for their primary healthcare needs, which contain different compound derived from medicinal plants.[6] For the determination of identity, purity and strength of the drug phytochemical standards are generally used in the herbal field. These parameters are also used to evaluate its genuine nature compared to the adulterated drugs. Phytochemical evaluation also plays an important role in the possible steps of adulteration.[7]

2. An overview of hispidulin

Hispidulin (4′, 5, 7-trihydroxy-6-methoxyflavone) is a naturally occurring flavone found in different plant materials such as *Saussurea involucrata* Kar. et Kir., a rare traditional Chinese medicinal herb, several Artemisia and Salvia species. Several in vitro studies have demonstrated its potent antioxidative, antifungal, anti-inflammatory, antimutagenic, and antineoplastic properties.[8,9] Recently, hispidulin is identified as a potent ligand of the central human benzodiazepine (BZD) receptor in vitro. It also acts as a partial positive allosteric modulator at γ-aminobutyric acid (GABA) receptors, penetrates the blood-brain barrier and possesses anticonvulsant activity in the central nervous system.[8,9] Hispidulin (Fig. 1) is the active compound which is also proven to be antimycobacterial, antiasthma, antimicrobial, antiproliferative, and insect larvicidal. This natural flavone is reported to be 100-fold more potent than theophylline in its property of inhibiting platelet aggregation.[10]

3. Pharmacological activities

3.1. Effect of hispidulin on cancers

Treatments of cancer have focused the main attention and interest of researchers due to their great impact on the human population's and health. A considerable ratio of deaths (2–3%) recorded worldwide annually due to different types of cancer.[3] Effect of hispidulin on its anti-tumor effect of Temozolomide (TMZ) in glioblastoma was studied and revealed that hispidulin enhanced the anti-tumor activity of TMZ in glioblastoma because of its inhibiting effect on cell proliferation and cell apoptosis induction.[11] Effect of the hispidulin, with sunitinib on renal cell carcinoma (RCC) cell proliferation in vitro and on in vivo tumor growth was studied. Hispidulin dose-dependently inhibited proliferation and induced apoptosis in both of the tested RCC cell lines. Inhibiting pStat3 signaling was found to be one of the main mechanisms for its antitumor activity. The result revealed that the combination treatment will be better therapeutic option for patients with RCC.[12] Gastric cancer is one of the most common malignant cancers due to poor prognoses and high mortality rates worldwide. Hispidulin inhibits the growth of gastric cancer cells through induced G1/S phase arrest and apoptosis in time- and concentration-dependent manners.[13] In another study, antiproliferative effects of hispidulin isolated from *Inula viscosa* (L.) were tested and were found to be active at the tested concentration.[3] Hispidulin significantly inhibited human pancreatic tumor growth in xenograft mice when treated at a dosage of 20 mg/kg daily. Further hispidulin also inhibited vascular endothelial growth factor (VEGF)-induced cell migration, invasion, and capillary-like structure formation in a dose-dependent manner.[14] Hispidulin potentiated the tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in human ovarian cancer cells and converted TRAIL-resistant cells to TRAIL-sensitive cells. Moreover hispidulin also downregulated the expression of Mcl-1, Bcl-2 and Bcl-xL.[15] *Glioblastoma multiforme* (GBM) is the most common and lethal type of primary brain tumor. Treatment of hispidulin resulted in dose-dependent inhibition of GBM cellular proliferation. Moreover, hispidulin-activated AMPK decreases the activity and expression of lipogenic enzymes, such as fatty acid synthase and acetyl-CoA carboxylase.[8] Effect of hispidulin on the cytotoxicity of the sesquiterpene lactone helenalin was studied in the human lung carcinoma cell line GLC4 using the microculture tetrazolium (MTT) assay. Hispidulin showed their modulating effect on helenalin-induced cytotoxicity in the significant range.[16] Mutagenicity and antimutagenicity of hispidulin were performed using the liquid preincubation method of the Salmonella test. At the highest dose tested, compounds showed no mutagenicity and no cytotoxicity toward *Salmonella typhimurium* strains TA98 and TA100 either in the presence or absence of S9 mix.[17] Hispidulin were evaluated for their inhibitory activity against LPS/IFN-γ-induced NO production in RAW 264.7 macrophages and for their cytotoxic activities against the human leukemic cell line CCRF-CEM and MRC-5 lung fibroblasts. Hispidulin markedly reduced LPS/IFN-γ-induced NO production in the tested cell lines.[18] In another study, hispidulin induces cell death in a dose and time-dependent manner in HepG2 cells whereas no toxic reaction was observed in normal human liver cells. Observed effect of hispidulin induces apoptosis in HepG2 cells suggested that the pro-apoptotic effect of Hispidulin was mediated through mitochondrial dysfunction and inhibition of P13k/Akt signaling pathway.[19]

3.2. Effect of hispidulin on radical system

Effects of hispidulin on the oxidative metabolism of isolated rat liver mitochondria were investigated. Hispidulin inhibited

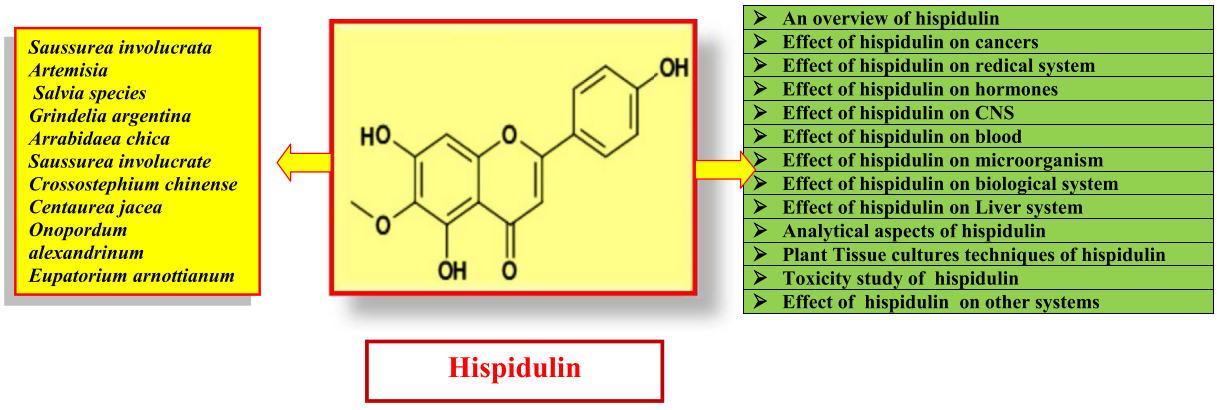

Fig. 1. Chemical structure and overview of hispidulin.