NOVEL EFFECTS OF DIOSGENIN –A PLANT DERIVED STEROID; A REVIEW

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Summary

Sapogenins are relatively cheap raw materials for the synthesis of a number of medicinally important steroids. Diosgenin is an aglycone of the steroidal saponin, dioscin, in yam and is a principal raw material for the industrial production of steroid drugs. It belongs to triterpene group and is of great interest to the pharmaceutical industry because of its estrogenic effect on the mammary gland. It plays an important role in cholesterol metabolism and it is responsible for morphological and biochemical changes in megakaryocyte cells. In this current review, we have focused on the potential effects of diosgenin and its pharmacological properties.

Keywords: Diosgenin, steroids, sapogenins, pharmacology.

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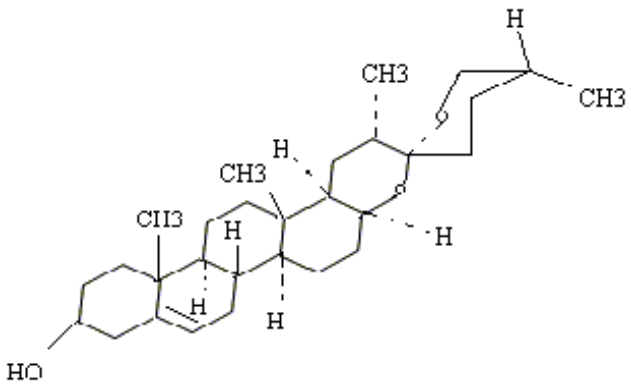
Introduction

Diosgenin [25R-spriost-5-en-3β-ol] is a hydrolysate of dioscin contained in the rootstock of yam and it exists widely in the natural plant such as glucoside (1). The discovery of diosgenin in the tubers of the yield yam has made it one of the most researched and studied herbal product. Many health benefits are associated with diosgenin, for example, prevention against cardiovascular disease, cancer and contraception (2, 3). Diosgenin is an important steroidal metabolite used as a starting material for the synthesis of steroidal drugs, as it exhibits estrogenic activity (4). Diosgenin has indicated effect of reducing the level of serum cholesterol (5, 6). It is mainly used as the initial material for partial synthesis of oral contraceptives, sex hormones and other steroids. Diosgenin has received considerable attention because of the variety of their promising pharmaceutical properties (7, 8). The consumption of diosgenin has positive actions on stress and inflammatory conditions.

Structure of Diosgenin



Source

Diosgenin is found in several plants, namely *Costus speciosus,Smilax menispermoidea*, *Trigonella, Trillium* and many species of *Dioscorea- D.althaeoides, colletti*, *zingiberensis* (9). In an extensive survey of 19 different species of Indian Dioscorea plants, Chakravarti et al. found *Dioscorea prazeri* (kokur torul) of Darjeeling and *Dioscorea deltoidea* (kins) of Kashmir are the rich sources of diosgenin.

Epidemiologic Studies

Diosgenin has been used in traditional Chinese medicine for treatment of urethral and renal infections (10). Diosgenin, made by hydrolysis of saponins, which were extracted from *Dioscorea villosa,* a plant which grows in North America, shows presumed ability to minimize post-menopausal symptoms (11). In Turkey, diosgenin is used as a good antispasmodic, that it can be used for cramps, coughs and for muscular spasms (12). A new Indian source for diosgenin is *Costus speciosus*, which is used to induce apoptosis in cancer cells and to reduce high blood pressure (13). Diosgenin extracted from *Trigonella foenum graecum* commonly called fenugreek, is a leguminous plant native to many Asian, Middle eastern & European countries, and is used as a hypoglycemic agent in type I and type II diabetes (14). Over the past decade a series of preclinical & mechanistic studies have been conducted worldwide to understand the role of diosgenin as a chemopreventive agent against several cancers.

Experimental studies

Diosgenin plays an important role in the cholesterol metabolism Roman et.al, fractionated the liver using diosgenin to elevate biliary cholesterol and found that diosgenin can be absorbed through gut. A lot of experiments had been conducted to show that diosgenin significantly induce apoptosis in various cell lines. Sahelian et al, studied the effects of sustained delivery of diosgenin on the adrenal gland of femal rats (15). The changes in body weight, organ weight and histopathological changes in the adrenal gland of rats were observed and it shows that reduction in adrenal mass may pose a potential for major endocrine complications. Zhony Yao Za Zhi investigated the antitumor activity of diosgenin in vivo and invitro. Tumor growth inhibit rates were calculated. He showed that diosgenin has an obvious antitumor activity on S-180, Hep A, U14 transplant mice in vivo and L 929, Hela, MCF cells invitro (16).

Extraction of diosgenin

Methods of extraction of diosgenin from *Dioscorea zinziberensis*, CH Wright include direct acid hydrolysis, spontaneous fermentation, supercritical CO_2 extraction and so on.

Recently, some researchers used a single enzyme such as cellulose, theamylase combined with acid hydrolysis to treat Chinese yam (Dioscorea opposite Thunb) material, demonstrating that about 70% diosgenin can be extracted from the material (17-20).

However, the activity of enzyme gradually reduces owing to the change of catalysis environment, so that the catalysis efficiency of enzyme will also reduce. Therefore it is urgent to find efficient methods to enhance the stability of natural cellulase. Current methods that enhance the stability of natural cellulose include selection, protein engineering, enzyme immobilization, enzyme chemical modification and adding a cosolvent agent (21).

Production of Diosgenin

Dioscorea zingiberensis is the dominant resource for the production of diosgenin. The main producing areas are Shiyan and Enshi of Hubei province, where more than 1500t of diosgenin are produced annually.

Dioscorea floribunda cells aggregates were cultured in liquid modified MS medium supplemented with 2,4-D(2mg/l) and kinetine(0.1 mg/l). The cells were treated with different concentrations of ethylene-generating agent 2-chloroethylphosphonic acid (2-CEPA). 2-CEPA at concentrations of 50 mg/l, 100 mg/l elicited production of diosgenin (22, 23).

Diosgenin-Quantification

The diosgenin concentrations in a *Dioscorea polygonoides* tuber collection from EC, Colombia were determined by HPLC and their percentages ranged from 0.02 to 2.64%. The average of diosgenin, recovery was 97%. Diosgenin was identified by gas chromatography-mass spectrometry (GC-MS) and coelution with authentic diosgenin standard in both HPLC and GC-MS techniques. It shows that *Dioscorea polygonoides* is a potential new source of diosgenin (24).

Bioactive Compounds derived from Diosgenin

By utilizing the intact skeleton of diosgenin, OSW-1 and its analogues were synthesized. Its anticancer activities are 10-100 times more powerful than some of the well known anticancer agents currently in clinical use, such as mitomycin C, adriamycin and taxol (25).

From readily available diosgenin, 16β-hydroxy-5α-cholestane-3,6-dione, a metabolite from marine algae was synthesized. It is a potent oxysterol, which exhibit a number of biological activities, including inhibition of cellular proliferation and cytotoxicity associated with induction of apoptosis (26).

Certonardosterol D_2, a polyhydroxysterol was stereoselectively synthesized from natural rich diosgenin, which posses a potent antitumor activity (27).

Regulation of Diosgenin Expression

Regulation of the diosgenin expression in *Trigonella foenum-graecum* plants by different plant growth regulators was studied. Treatment with 10^{-5} and 10^{-4} M gibberelic acid led to 43% and 19% increases, respectively of diosgenin in 30-day-old whole plants. These increases might be associated with the action that this growth regulator has in stimulating plant growth and the biosynthetic pathway of this sapogenin. A similar increase was obtained with the 10^{-5}M indole-3-acetic acid treatment. Treatment with 50 ppm ethepon increased the diosgenin levels observed in the leaves of 15 and 30-day-old plants, growth of the whole plant being substantially reduced at 30 days in comparison with the growth observed in control plants (28).

Dose

The amount of diosgenin to be administered per day is in the range 100 to 2000 mg, preferably 150 to 1200 mg, most preferably 300 to 1200 mg. This amount may be administered in a single dose or in more than one dose which may be taken at different times throughout the day.

Pharmacological properties of Diosgenin

Hypoglycemic activity

Consumption of commercial diosgenin demonstrated hypoglycemic properties, which are beneficial in diabetes by reducing intestinal disaccharides activities. It has been reported using experimental studies in diabetic male wistar rats, where there is a significant increase in lactase and maltase activities, reduced intestinal sucrose activity. The activity of glucose -6- phosphate was significantly increased (29).

Hypolipidemic and Antioxidant Activity

Oxidative stress has been suggested as a main risk factor in the development of atherosclerosis. Diosgenin enhanced the resistance to lymphocyte DNA damage caused by an oxidant challenge with H_2O_2.The hypolipidemic and antioxidative effect on rats fed with a high-cholesterol diet supplemented with either 0.1% or 0.5% diosgenin for 6 weeks has been investigated. Diosgenin showed a decrease in the plasma and hepatic total cholesterol levels (30).

Neuroprotective Activity

Human Immuno deficiency virus (HIV) infection continues to rise in drug-abusing populations and causes a dementing illness in a subset of individuals. In-vitro studies showed that HIV proteins, gp120 and Tat, Tat + morphine caused increased neurotoxicity in human neuronal cultures with ApoE4 allele. A number of novel antioxidants has been screened and found that only L-deprenyl and diosgenin protected against the neurotoxicity of Tat + morphine (31).

Vasodilating Activity

Diosgenin is structurally "fairly similar" to progesterone. It is the precursor for the industrial large scale synthesis of different hormones including progesterone and norethisterone. The vasodilating effect of diosgenin was studied and it shows an acute, endothelium independent coronary artery relaxation (32).

Role in Cholesterol Metabolism

Diosgenin, structurally similar to cholesterol, has been shown to decrease cholesterol absorption and to increase biliary cholesterol secretion without altering either serum cholesterol or total biliary bile salt secretion (33). It has been reported that increased biliary secretion of cholesterol and lipid vesicles induced by diosgenin, has cytoprotective effects in the rat liver subjected to obstructive cholestasis (34).

Role in Melanogenesis

An increased level of melanin is characteristic of a large number of skin disease, including acquired hyperpigmentation conditions such as melasma, post inflammatory

melanoderma and solar lentigo. Diosgenin inhibits the melanin content significantly (35). Skin aging is a consequence of both programmed aging that occurs with time and aging caused by environmental factors such as exposure to ultraviolet rays. The supplementation of natural or synthetic diosgenin has anti-aging approaches (36).

Role of Diosgenin in Cell Cycle Arrest and Apoptosis in Cancer Cell Lines

Treatment of tumor cells with cytotoxic agents usually results in the breakdown of the cell cycle machinery, the cells subsequently entering into programmed cell death or apoptosis. Diosgenin plays a significant role in apoptosis. Diosgenin can inhibit proliferation via blocking cell cycle progression at the G_2/M phase and subsequently progression to apoptosis in human leukemia K562 cells. Diosgenin can effectively inhibit the viability and proliferation of breast cancer cells MCF-7 (37). Diosgenin induces differentiation of human erythroleukemia cell line (HEL TIB 180) through changing lipoxygenase activities. It also has been reported to induce apoptosis and cell cycle arrest in human osteosarcoma 1547 cell line. Diosgenin induced Hela cell apoptosis through caspase pathway (38).

Cyclooxygenase(COXs) are key enzymes in the conversion of arachidonic acid into prostanoids which are involved in apoptosis and inflammation. Two distinct COXs have been identified, COX-1 which is constitutively expressed and COX-2 which is induced by different products such as tumor promoter or growth factors. Diosgenin, induces apoptosis and its effects were tested on COX expression and activity in osteosarcoma cells (39). Rheumatoid arthritis (RA) is an inflammatory joint disease in which perpetuation of chronic synovitis leads to bone and cartilage degradation. Diosgenin causes an inhibition of the growth of fibroblast like synoviocytes from human rheumatoid arthritis, with apoptosis induction associated with cyclooxygenase-2 up-regulation (40). Colon cancer is considered a preventable disease. However, there seems to be no decline in the incidence of colon cancer and many of the risk factors associated with colon cancer prevail. In-vitro experiments indicated that diosgenin inhibits cell growth and induces apoptosis in the HT-29 human colon cancer cell line in a dose-dependent manner (41). Fatty acid synthase (FAS) expression is markedly elevated in HER 2-overexpressing breast cancer cells. In this, diosgenin found to be effective in suppressing FAS expression in HER 2-overexpressing breast cancer cells and preferentially inhibited proliferation and induced apoptosis in HER 2-overexpressing cancer cells (42).

Adverse Effect

As an herbal extract, diosgenin appears to be free of any major adverse effects (43).

Conclusion

Large number of studies have revealed that diosgenin posses therapeutic actions such as anti-inflammatory, anticancer. Its anti-inflammatory activity is mainly due to COX activity. Diosgenin is reported to stabilize lysosomal membrane and causes uncoupling of oxidative phosphorylation and having strong oxygen radical scavenging activity. Most interesting feature of diosgenin is lack of intestinal side effects, thus it is used in the synthesis of oral contraceptives, sex hormones. More recent work is needed in order to explore its new areas of application.

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