Pharmacological characteristics of a phytosteroidal food saponin: Diosgenin

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Abstract

Diosgenin, a plant derived steroidal saponin found most abundantly in legumes and yams. It has been used for the treatment of various types of disorder such as leukemia, inflammation, hypercholesterolemia and cancer. Besides being a lactation aid, it has been shown to be gastro- and hepato-protective, antioxidant, antidiabetic and vaso-dilatory compound. It is a precursor for production of several steroidal hormones. This review focuses on the pharmacological properties of diosgenin, a food saponin.

Keywords: Diosgenin, Phytosteroid, Food saponin, Traditional medicine, Steroidal sapogenin.

1. Introduction

Nature has been a source of medicinal products and for thousands of years many helpful drugs have been created from plant sources (Cragg and Newman, 2013). Plants provide a big reservoir of natural products used throughout the history of civilization as the primary source of medicine (Yan et al., 2015). In vitro and animal data showed that many dietary phytochemicals have powerful chemopreventive activities. Single-agent compounds, however, have produced conflicting yield in humans (Kotecha et al., 2016). Food saponins were used for a multitude of diseases in complementary and traditional medicine (Raju and Rao, 2012). Saponins have gained significant attention in latest years due to their multiple biological activities (Kaskiw et al., 2009).

Natural wealthy plant sapogenins are comparatively inexpensive raw materials for the synthesis of a number of medicinally significant steroids (Deshpande and Bhalsing, 2014). Because of their broad bioactivity properties, saponins are highly attractive. As a consequence, different techniques have been used to improve medicinal plants' phytochemical composition. The significant families that biosynthesize steroidal sapogenins are Agavaceae (genus Agave), Dioscoreae (genus Dioscorea) and Liliaceae (genera Allium, Asparagus, Lilium) (Niño et al., 2007). Saponins classified by their carbon skeletons into triterpenes and steroids (Vincken et al., 2007). In common vegetable foods and products for human consumption, plant steroids such as diosgenin(D), sitosterol, tomatodin, soyasaponin, digitonin, and others are found (Accatino, 1998). In particular, Diosgenin is a major active ingredient in a variety of traditional and patented Chinese medicines (Nie et al., 2016).

Diosgenin(3β,25R)-spirost-5-en-3-ol, is a spirostanol saponin with hydrophilic sugar moiety associated with hydrophobic steroid aglycone (Raju and Rao, 2012). It is a natural steroid sapogenin, a dioscin hydrolysate...
found mostly in fenugreek, legumes (Trigonella sp.) and yams (Dioscorea sp.). In 1935 in Dioscorea Tokoro Makino, Fujii and Matsukawa first discovered the diosgenin (Yan et al., 2015). It is structurally similar to cholesterol and some other steroids. It is a precursor of various synthetic steroidal drugs that are widely used in the pharmaceutical industry such as cortisone, pregnenolone, progesterone, etc., and also in the synthesis of several hormones such as testosterone, norethisterone, glucocorticoids and progesterone (Chaudhary, 2018). Several sources of plant products have been used to isolate diosgenin, including dioscorea, costus and trigonella. Dioscorea species are economically essential as staple food and other species are used to create steroidal saponins that cause hydrolysis of sapogenins such as diosgenin (Jesus, 2016). Yams belong to genus Dioscorea, with nearly 400 species growing in the tropical and subtropical wetlands worldwide. This family has been defined by the manufacturing of underground or aerial tubers. Its species generally climb trees, many of which are dioicous. Diosgenin is reported as a promising bioactive biomolecule with various pharmacological properties such as anticancer, antidiabetes, cardiovascular protective, immunomodulatory and skin protective effects as shown in preclinical studies (Yan et al., 2015). Consequently, diosgenin has in latest years drawn significant attention in the pharmaceutical, functional food and cosmetics sectors (Kim, 2018). Recently, diosgenin’s medicinal property has been increased to include life-threatening disease treatment (Kalalingam et al., 2014). Hence diosgenin with a wide number of clinical applications is

| Table 1: Physico chemical properties of diosgenin |
|-----------------------------------------------|
| Nature of diosgenin | Values |
| Color | Colorless |
| Odor | Odorless |
| Solubility | Soluble in organic solvents, acetic acid. Not soluble in water |
| Molecular weight | 414.62 |
| Physical state | White to off-white crystalline powder |
| Density | 1.13 |
| Log P | 6.34 |
| Chemical formula | C_{27}H_{42}O_{3} |

Source: https://en.wikipedia.org

1 Yam dioscorea alata: Topics by Science.gov https://www.science.gov/topicpages/y/yam+dioscorea+alata)
considered as a potentially useful drug. In this review, we focus the results from clinical, animal and in vitro studies investigating diosgenin’s pharmacological aspects.

1. Epidemiologic studies

Diosgenin in sanyaku, a traditional Chinese medicine present in yam tubers as food is used to treat human colon cancer (Miyoshi et al., 2011). Diosgenin is native to North America and has been commonly used as a natural option for estrogen replacement therapy to enhance women’s health and treatment with inflammation, muscle spasm and asthma (Manda et al., 2013). Diosgenin is used in Turkey as a useful antispasmodic to be used for cramps, coughs and muscle spasms (Nigam, 2018). Costus speciosus, is a fresh Indian source for diosgenin, which is used to cause apoptosis in cancer cells and decrease high blood pressure. Diosgenin obtained from Trigonella foenum graecum, frequently referred to as fenugreek, is a leguminous plant indigenous to many Asian, Middle Eastern and European nations and is used as a Type-I and Type-II diabetes hypoglycemic agent (Mirunalini and Shahira, 2011).

![Figure 2: Pharmacological properties of diosgenin](https://www.sciencedirect.com/journal/steroids/vol/118/suppl/C)

2. Pharmacological activities

Pharmacological efficacy is a drug’s capacity under controlled circumstances to generate a required therapeutic effect. Correspondingly, diosgenin also has a wide variety of pharmacological activities such as anticancer, antidiabetes, anti-infectious, neuroprotective, anti-inflammatory, etc.

2.1. Activity on cancer

Diosgenin’s mode of action against cancer has been demonstrated by modulating multiple cell signaling events involving critical molecular candidates associated with growth, differentiation, apoptosis and oncogenesis (Raju and Mehta, 2008). Several preclinical studies have shown that diosgenin inhibits tumor cell proliferation and induces apoptosis (He et al., 2014).

Diosgenin inhibited cells of the human colon adenocarcinoma HT-29 and HCT-116 growth (Raju and Mehta, 2008). It also induced a significant transwell assay inhibition of cell migration in MDA-MB-231 cells. Furthermore, under real-time observation, MDA-MB-231 cell migratory behavior was significantly impacted by diosgenin. It significantly suppresses actin polymerization and Vav2 phosphorylation, which plays a significant part in the development of breast cancer, thereby reducing Cdc42 activation in human breast cancer MDA-MB-231 cells, which can be attributed to the anti-metastatic potential of diosgenin (He et al., 2014). Furthermore, it was found to trigger cell cycle arrest associated with strong apoptosis in vitro against human 1,517 osteosarcoma cells unlike its two structurally identical saponins, hecogenin and tigogenin (Steroids | Vol 118, Pages 1-128 (February 2017) | ScienceDirect.comhttps://www.sciencedirect.com/journal/steroids/ vol/118/ suppl/C). It may improve cytotoxicity in HER-2 overexpressing-cancer cells caused by paclitaxel. Consequently, it can progress as a chemo preventive or chemotherapeutic agent for cancers.
overexpressed by HER-2 (Chiang et al., 2007). The oxidative peak observed at +0.75 in potentiometric stripping analysis on the graphite electrode showed that diosgenin can effectively inhibit breast cancer cell viability and proliferation (Li et al., 2005). Moreover, it was also reported to inhibit proliferation of ER-positive MCF-7 breast cancer cells by upregulating the p53 tumor suppressor gene and activating caspase 3, while downregulating BCL2 in ER-negative MDA-MB-231 triple-negative breast cancer cells (Srinivasan et al., 2009). In addition, diosgenin powerfully suppressed phosphorylation of phosphatidylinositol-3-kinase (PI3K), Akt, extracellular signal regulating kinase (ERK), c-jun and N-terminal Kinase (JNK) and inhibited dose-dependent proliferation of PC-3 cells (Chen et al., 2011). By suppressing the Hepatocyte Growth Factor (HGF)—caused epithelial—mesenchymal transformation by Mdm2 and vimentin reduction, it also inhibits DU145 proliferation (Chang et al., 2011). The diosgenin-derivative 26-hydroxy-22-oxocholestanic steroid in human cervical cancer CaSki cells causes apoptosis at non-cytotoxic doses of caspase-3 activation (Fernández-Herrera et al., 2010). Furthermore, it caused the Hepatocellular Carcinoma (HCC) cells to be arrested during the GI phase of the cell cycle and caused apoptosis by caspase-3 activation leading to PARP cleavage. It also inhibited both constitutive and inductive activation of signal transducers and transcription activators (STAT3) in these cells with no effect on STAT5 and suppressed the activation of c-Src, Janus-family tyrosine kinases (JAK)1 and JAK2 involved in STAT3 activation (Raju and Rao, 2012).

While diosgenin may inhibit proliferation of cancer cell in vitro, some experimental studies have reported that diosgenin also inhibits proliferation of cancer cells in vivo. It inhibited colon aberrant crypt foci (ACF), putative azoxymethane (AOM), which caused precancerous lesions in rats F344. During initiation/post-initiation or promotional phases, the administration of diosgenin in the diet at a dose of 0.1% and 0.05% (wt/wt) significantly suppressed AOM-induced colon ACF (Raju et al., 2004). Malisetty et al. (2005) found that 0.1% of diosgenin suppressed up to 60% of the incidence of invasive and non-invasive colon adenocarcinomas by. Furthermore, compared to controls diosgenin decreased the multiplicity of colon tumors (adenocarcinomas/rat). In part, these in vivo impacts have been shown to be associated with a reduced PCNA index in colon tumors, indicating that diosgenin reduces the proliferation of tumor cells (Malisetty et al., 2005). It inhibits the expression of pAkt and Akt kinase without influencing the concentrations of PI3 kinase, thereby inhibiting its downstream objectives, NF-Kb, Bcl-2, survivor and XIAP. In vivo tumor studies shown that diosgenin (10mg/kg intra-tumoral body weight) significantly inhibits tumor growth in both MCF-7 and MDA-231 xenografts in nude mice (Srinivasan et al., 2009). It has recently been revealed to be efficient against experimentally caused inflammation associated with colon carcinogenesis in ICR mice, considerably decreasing tumor multiplicity by modifying lipid metabolism (decreased serum triglyceride concentrations by up-regulation of lipoprotein lipase) and modulating genes connected with inflammation and various signaling pathways (Miyoshi et al., 2011).

2.2. Activity on diabetes

Studies promote the potential of diosgenin in the management of diabetes by enhancing oxidative stress and lipid metabolism dysfunction. In addition, fenugreek rich source of diosgenin improves hepatic steatosis and hyperlipidemia in the obese diabetic mice by suppressing the lipogenic gene expression of mRNA (Yan et al., 2015). In addition, impacts of diosgenin in streptozotocin-induced diabetic rats were researched in blood glucose and intestinal amylase and ATPases. The activity of α-amylase improved considerably in the proximal area of the tiny intestinal mucosa of diabetic rats treated with diosgenin. In fasting blood glucose, reduced
activity of Na\(^{+}\)-K\(^{+}\)-ATPase, Ca\(^{2+}\)ATPase activity was also found in the proximal region compared to diabetic control (McAuff et al., 2005). As the substance responsible for the fenugreek inhibitory impact, diosgenin inhibits the accumulation of triglyceride (TG) and lipogenic gene expression in HepG2 cells, which adds to the therapeutic impacts of fenugreek on lipid metabolism illnesses (Uemura et al., 2010). Recently, diosgenin’s effects on enzyme levels have been investigated. Plasma glucose and glucose-6-phosphatase levels reduced considerably in diabetic rats fed with diosgenin relative to diabetic control. Activities in the liver of diabetic rats of ATP-citrate lyase, pyruvate kinase and glucose-6-phosphate dehydrogenase were considerably decreased in comparison with ordinary control (McAuff et al., 2005). Analysis of lipid accumulation in 3T3-L1 preadipocytes has shown that diosgenin (levels varying from 0.1 to 10 \(\mu\)mol. L\(^{-1}\)) can encourage PPAR\(\gamma\) expression and differentiation of adipocytes, which can assist decrease circulating lipids in the blood and lead to hypolipidemic activity in Type-2 diabetes rats (Sangeetha et al., 2013). It has demonstrated the ability to produce anti-diabetic effects that mitigate hyperglycemia and insulin resistance and mitigate metabolic dysregulation of the lipid profile in plasma and tissue (Naidu et al., 2015).

2.3. Activity on cardiovascular disease

The preconditioning with diosgenin may induce cardioprotective action against reperfusion injury by reducing inflammatory mediator production and activating the mitoATP channels (Ebrahim et al., 2014). Furthermore, diosgenin pretreatment (80 mg/ kg) reversed the activity of member-bound proteins and thus preserved standard electrolyte concentration indicates the protective action of diosgenin in ISO-induced myocardial infarction (Jayachandran et al., 2009). Diosgenin can cause endothelial-independent vascular relaxation, involving several fundamental processes, such as in vitro and in vivo protection of the vasculature from oxidative stress (Manivannan et al., 2013). It also inhibited the angiotensin II by suppressing the transforming growth factor \(\beta1/\) Smad3 signaling pathway induced extracellular matrix remodelling in cardiac fibroblasts of rats. Therefore, it may have therapeutic potential for cardiac fibrosis treatment (Zhou et al., 2017). Moreover, it modulates the opening and reduced oxidative stress of mitochondrial ATP-sensitive potassium channels. These activities may contribute to the cardioprotective effect of diosgenin in injury caused by ischemia-reperfusion (Badalzade et al., 2017). It is a very helpful compound for managing hyperlipidemia by enhancing the lipid profile as well as modulating oxidative stress and preventing \(H_2O_2\)-induced apoptosis of human vein endothelium cells (HUVEC’s), partly by regulating mitochondrial dysfunction pathways (Gong et al., 2010). It also interferes with both exogenous and endogenous absorption of cholesterol; this interference is followed by enhanced rates of hepatic and intestinal cholesterol synthesis. The enhanced unabsorbed cholesterol and enhanced secretion of bile cholesterol led to enhanced excretion of neutral sterols without bile acid and fecal excretion (Cayen and Dvornik, 1979). In addition, due to an oxidant \(H_2O_2\) challenge, diosgenin feeding enhanced resistance to lymphocyte DNA damage. Supplementation with diosgenin also affected the operations of antioxidant enzymes. Total superoxide dismutase (TSD) in plasma and liver, glutathione peroxidase (GSH-Px) in erythrocytes, and catalase (CAT) in erythrocytes and liver were significantly increased in the 0.5% diosgenin group. It also up-regulates the expression of antioxidant enzymes, with GSH-Px being the largest concentration in the diosgenin group of 0.5%. Consequently, the reports indicate that diosgenin can be a very helpful compound to control hypercholesterolemia by enhancing the lipid profile and modulating oxidative stress (Son et al., 2007).

2.4. Activity on neuroprotection

Diosgenin selectively suppressed the production/ expression of pro-inflammatory M1 markers by activated microglia without influencing M2 markers and could provide neuroprotection by controlling microglial M1 polarization (Wang et al., 2017). It has been shown to increase nerve growth factor levels in the diabetic rat’s sciatic nerve, neurite outgrowth in PC12 cells, and to increase nerve conductivity in a diabetic mouse model (Kang et al., 2011). Moreover, it may affect currents in human cortical neurons (HCN -1A) by modulating large-conductance Ca\(^{2+}\)-activated K\(^{+}\) channel with an \(EC_{50}\) value of 25 \(\mu\)mol L\(^{-1}\) that may affect cortical neuron functional activity (Wang et al., 2006). Additionally, it was an ischemia-reperfusion-induced injury neuroprotective. This impact involved anti-apoptotic and anti-inflammatory activity as well as modulation of the signaling pathway characteristics of the nuclear factor \(-\)KB (Zhang et al., 2016). It has been shown in a purified rat oligodendrocyte progenitor cell (OPC) culture model to promote the OPC differentiation through an ERK1/2 activation pathway mediated by an estrogen-receptor to enhance remyelination, thus protecting the normal function of neurons (Xiao et al., 2012). Recently, diosgenin administration significantly improves D-gal treated mice’s learning and memory skills, which can be partially mediated by enhancing endogenous antioxidant enzymatic activities (Chiu et al., 2011).
2.5. Activity on immunological system

Diosgenin improves allergic diseases primarily by regulating the immune response of T-cells. Diosgenin suppresses allergen-induced response of the intestinal Th2 by improving the regulatory immunity of T-cells in BALB/c, ovalbumin sensitized mice (OVA) (Huang et al., 2010). Oral diosgenin reduced the production of IgE and allergic intestinal inflammation in the food allergy murine model (Huang et al., 2009). Although its consumption modulates certain elements of the acquired immunity, including the improvement of antigen-specific IgG2a and IFN-γ expression, which can be mediated by Th1 differentiation up-regulation (Ian et al., 2007). It also decreases the output of inflammatory mediators by inhibiting the activation of CK2, JNK, NF-κB and AP-1 triggered LPS/IFN, thus involving a mechanism through which diosgenin can exert its immunosuppressive impacts (Jung et al., 2010). In addition, it could stimulate the transformation of lymphocytes and enhance the phagocytic capacity of intracellular macrophages, promoting the secretion of NO and TNF-α in macrophages significantly. Moreover, diosgenin could improve specific and non-specific cellular immune responses and that diosgenin’s anti-tumor effect were achieved by immunostimulant properties rather than by direct cytotoxicity (He et al., 2012). It also inhibits cell proliferation, arrested G0/G1 and was able to inhibit IGF-1-induced cell proliferation in primary human thyroid cells (Bian et al., 2011). Recently, plant steroid diosgenin inhibits the growth of fibroblast-like synoviocytes from human rheumatoid arthritis with cyclooxygenase-2 (COX-2)–associated apoptosis induction. In addition, diosgenin’s proapoptotic effect is associated with COX-2 overexpression correlated with endogenous prostaglandin E2 overproduction. It was screened with RBL-2H3 cells for anti-allergic activity and the aglycone was discovered to be more active than the diglucosylated molecule (Patel et al., 2012).

2.6. Activity on skin protection

Diosgenin can improve the synthesis of DNA and increase the proliferation of keratinocytes by causing AMP signals without involving receptors of estrogen. Diosgenin administration (0.01%, 0.02%, 0.04% blended with basal intake) increases the epidermal density of a climate-character mouse model (Tada et al., 2009). In addition, diosgenin (1-50 μmol. L-1) inhibits melanogenesis by activating the P13 K pathway in B16 melanoma cells, indicating that diosgenin can be an efficient inhibitor of hyperpigmentation in the therapy of skin illnesses such as acquired hyperpigmentation circumstances (Lee et al., 2007).

2.7. Activity on reproductive system

Diosgenin seems to boost the development and activation of primordial follicles. Old mice treated with diosgenin could therefore improve the ovarian reserve. NOBOX (fresh homeobox ovary protein) has been expressed in oocytes and GDF9 has been expressed in granulosa cells in increasing follicles. Diosgenin seems to boost the development and activation of primordial follicles. Old mice treated with diosgenin could therefore improve the ovarian reserve. NOBOX (fresh homeobox ovary protein) has been expressed in oocytes and GDF9 has been expressed in granulosa cells in increasing follicles. Nevertheless, the amount of main, primary, and secondary follicles in the DHEA group improved slightly insignificantly. DHEA seemed to increase the number of pre-antral follicles to some extent, but in our study, it did not improve the recovery of MII oocytes or promote oocyte quality. This may be associated with reduced NOBOX expression and increased DHEA expression of GDF9. Thus, diosgenin raises the number of main follicles, thereby encouraging ovarian reserve in a mouse model (Shen et al., 2017). It also leads to late activation of transcriptional nuclear ESR activity, which in turn directly controlled the cycle of apoptosis-related cells and variables such as cyclin D and Bcl-2. Therefore, it demonstrates that SRC-ESR translocation-ERK/ Akt-ESR transcriptional activity was activated by diosgenin, resulting in cell cycle transformation and inhibition of apoptosis and thus final cell proliferation. These results can enhance our knowledge of the pharmacological actions of diosgenin and advance therapeutic solutions to male infertility (Wu et al., 2015).

2.8. Activity on blood system

An anti-thrombosis impact of diosgenin was explored using a model of reduced vena cava ligation thrombosis rat and pulmonary thrombosis mice in vitro and in vivo, resulting in dose-dependent inhibited platelet aggregation, thrombosis and extended partial activated thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) in rats. Bleeding time, coagulation time is also extended along with an increased rate of protection in mice, which revealed anti-thrombosis activity (Gong et al., 2011).
Table 2: Pharmacological activities of diosgenin

| Pharmacological Activities                                                                 | Reference                  |
|-------------------------------------------------------------------------------------------|----------------------------|
| Induce autophagy and apoptosis in human prostate cancer cell line                          | Nie et al. (2016)          |
| Inhibits the migration of human breast cancer MDA-MB-231 cells                             | He et al. (2014)           |
| Suppresses fatty acid synthase expression in HER-2 overexpressing breast cancer cells     | Chiang et al. (2007)       |
| Induces DNA damage and apoptosis in DU145 prostate cancer cells                            | Chen et al. (2011)         |
| Suppresses hepatocyte growth factor (HGF) induced epithelial-mesenchymal transition       | Chang et al. (2011)        |
| Induces apoptosis in HT-29 human colon cancer cells.                                       | Raju et al. (2004)         |
| Decreases plasma and hepatic triglycerides in obese diabetic mice                          | Uemura et al. (2010)       |
| Inhibits angiotensin-II induced extracellular matrix remodeling in cardiac fibroblasts     | Zhou et al. (2017)         |
| Prevents high glucose-induced cardiomyocytes apoptosis                                    | Pi et al. (2017)           |
| Provides neuroprotection by regulating microglial M1 polarization                          | Wang et al. (2017)         |
| Enhances regulatory T-cell immunity                                                       | Huang et al. (2010)        |
| Inhibits melanogenesis through the activation of PI3K signaling pathway                    | Lee et al. (2007)          |
| Exhibits antiviral activity in vitro against hepatitis C virus                             | Wang et al. (2011)         |

2.9. Activity on infectious agents

Diosgenin has been explored for its anti-infectious impacts against fungi, bacteria, protozoa, and virus. An antifungal activity against candida albicans, human pathogenic species, C. Glabrata, C. Tropicalis showed weak antimicrobial activity of this steroid against all the species tested (Sautour et al., 2004; and Yang et al., 2006). Also, it has a low to null effect against the fungi Aspergillus flavus, Aspergillus niger, Trichoderma harzianum, and Fusarium oxysporum. When studied with multiple Gram-positive pathogens (Bacillus subtilis, Bacillus cereus, Staphylococcus aureus and Staphylococcus epidermidis) and Gram-negative pathogens (Escherichia coli and Salmonella typhi), this sapogenin showed important inhibition area (Khan et al., 2015). In addition, its antiamoebial activity against Naegleria fowleri trophozoites was also explored at the molecular and cellular levels. Interestingly, anti-surface membrane activity and NF cysteine protease of trophozoites of fowleri have been suggested. In addition, this steroid’s therapeutic toxicity to mammalian cells was smaller than that of the drug amphotericin B presently used to treat Na. Infections of fowlers (Rabablert et al., 2015). In addition, in some instances it has been shown to be an exciting molecule in certain viral diseases. Because of its antioxidant activity, it can also be helpful in HIV patients with dementia (Turchan et al., 2003). This steroid also demonstrates antiviral activity against Hepatitis C Virus (HCV) in in vitro research. Since it can decrease plasma cholesterol and HCV needs cholesterol to replicate efficiently, viral replication inhibition can be correlated with this impact (Wang et al., 2011).

3. Conclusion

Diosgenin is a biologically active ingredient in sanyaku, a traditional Chinese medicine that is yam tuber (Dioscorea) freeze-dried powder and yam has been used for a long time as a botanical dietary supplement to maintain or improve health. This review indicates that diosgenin is a promising bioactive biomolecule with a range of significant medicinal properties including anticancer, anti-diabetes, protective cardiovascular, neuroprotective, immunomodulatory, and protective impacts on the skin. Therefore, diosgenin is a potential molecule of concern in prevention/treatment of various diseases. The high potential of this compound, its analogs or combination of this compound with other compounds had already been demonstrated. However, carrier systems such as nanoparticles need to be developed to guide them where diosgenin operates to enhance efficacy and eventually decrease side effects. In conclusion, several difficulties need to be overcome, such as the creation of fresh delivery technologies, pharmaceutical formulations and water-soluble semi-synthetic...
derivatives, in order to uncover the advantages of either diosgenin as a preventive/therapeutic chemotherapy agent.

References

Accatino, L., Pizarro, M., Solís, N. and Koenig, C. S. (1998). Effects of diosgenin, A plant-derived steroid, on bile secretion and hepatocellular cholestasis induced by estrogens in the rat. Hepatology. July. 28(1), 129-140.

Badalzadeh, R., Tabatabaei, S. M., Mohammadi, M., Khaki, A. and Mohammadnejad, D. (2017). Combined postconditioning with ischemia and cyclosporine-A restore oxidative stress and histopathological changes in reperfusion injury of diabetic myocardium. Iranian Journal of Basic Medical Sciences. October. 20(10), 1079.

Bian, D., Li, Z., Ma, H., Mu, S., Ma, C., Cui, B., Gao, L. and Zhao, J. (2011). Effects of diosgenin on cell proliferation induced by IGF-1 in primary human thyrocytes. Archives of Pharmacal Research. June 1. 34(6), 997-1005.

Cayen, M. N. and Dvornik, D. (1979). Effect of diosgenin on lipid metabolism in rats. Journal of Lipid Research. February 1. 20(2), 162-174.

Chang, H. Y., Kao, M. C., Way, T. D., Ho, C. T. and Fu, E. (2011). Diosgenin suppresses hepatocyte growth factor (HGF)-induced epithelial-mesenchymal transition by down-regulation of Mdm2 and vimentin. Journal of Agricultural and Food Chemistry. May 2. 59(10), 5357-5363.

Chaudhary, S., Chaudhary, P. S., Chikara, S. K., Sharma, M. C. and Iriti, M. (2018). Review on fenugreek (Trigonella foenum-graecum L.) and its important secondary metabolite diosgenin. Notulae Botanicae Horti Agrobotanici Cluj-Napoca. January 1. 46(1), 22-31.

Chen, H. M., Chang, F. R., Hsieh, Y. C., Cheng, Y. J., Hsieh, K. C., Tsai, L. M., Lin, A. S., Wu, Y. C. and Yuan, S. S. (2011). A novel synthetic protoapigenone analogue, WYC02-9, induces DNA damage and apoptosis in DU145 prostate cancer cells through generation of reactive oxygen species. Free Radical Biology and Medicine. May 1. 50(9), 1151-1162.

Chiang, C. T., Way, T. D., Tsai, S. J. and Lin, J. K. (2007). Diosgenin, a naturally occurring steroid, suppresses fatty acid synthase expression in HER2overexpressing breast cancer cells through modulating Akt, mTOR and JNK phosphorylation. FEBS Letters. December 22. 581(30), 5735-5742.

Chiu, C. S., Chiu, Y. J., Wu, L. Y., Lu, T. C., Huang, T. H., Hsieh, M. T., Lu, C. Y. and Peng, W. H. (2011). Diosgenin ameliorates cognition deficit and attenuates oxidative damage in senescent mice induced by D-galactose. The American Journal of Chinese Medicine. 39(03), 551-563.

Cragg, G. M. and Newman, D. J. (2013). Natural products: a continuing source of novel drug leads. Biochimica et Biophysica Acta (BBA)-General Subjects. June 1. 1830 (6), 3670-3695.

Deshpande, H. A. and Bhalsing, S. R. (2014). Plant derived novel biomedicinal: diosgenin. Int. J. Pharmacogn. Phytochem. Res. 6, 780-784.

Ebrahimih, H., Badalzadeh, R., Mohammadi, M. and Yousefi, B. (2014). Diosgenin attenuates inflammatory response induced by myocardial reperfusion injury: role of mitochondrial ATP-sensitive potassium channels. Journal of Physiology and Biochemistry. June 1. 70(2), 425-432.

Fernández-Herrera, M. A., Mohan, S., López-Muñoz, H., Hernández-Vázquez, J. M., Pérez-Cervantes, E., Escobar-Sánchez, M. L., Sánchez-Sánchez, L., Regla, I., Pinto, B. M. and Sandoval-Ramírez, J. (2010). Synthesis of the steroidal glycoside (25R)-3α, 16α-diacetoxy-12, 22-dioxo-5α-cholestan-26-yl α-d-glucopyranoside and its anti-cancer properties on cervicouterine HeLa, CaSk, and ViBo cells. European Journal of Medicinal Chemistry. November 1. 45(11), 4827-4837.

Gong, G., Qin, Y. and Huang, W. (2011). Anti-thrombosis effect of diosgenin extract from Dioscorea zingiberensis CH Wright in vitro and in vivo. Phytomedicine. April 15. 18(6), 458-463.

Gong, G., Qin, Y., Huang, W., Zhou, S., Wu, X., Yang, X., Zhao, Y. and Li, D. (2010). Protective effects of diosgenin in the hyperlipidemic rat model and in human vascular endothelial cells against hydrogen peroxide-induced apoptosis. Chemico-Biological Interactions. March 30. 184(3), 366-375.
He, Z., Chen, H., Li, G., Zhu, H., Gao, Y., Zhang, L. and Sun, J. (2014). Diosgenin inhibits the migration of human breast cancer MDA-MB-231 cells by suppressing Vav2 activity. Phytomedicine. May 15. 21(6), 871-876.

He, Z., Tian, Y., Zhang, X., Bing, B., Zhang, L., Wang, H. and Zhao, W. (2012). Anti-tumour and immunomodulating activities of diosgenin, a naturally occurring steroidal saponin. Natural Product Research. December 1. 26(23), 2243-2246.

Huang, C. H., Ku, C. Y. and Jan, T. R. (2009). Diosgenin attenuates allergen-induced intestinal inflammation and IgE production in a murine model of food allergy. Planta Medica. October. 75(12), 1300-1305.

Huang, C. H., Liu, D. Z. and Jan, T.R. (2010). Diosgenin, a plant-derived sapogenin, enhances regulatory T-cell immunity in the intestine of mice with food allergy. Journal of Natural Products. May 13. 73(6), 1033-1037.

Jan, T.R., Wey, S.P., Kuan, C.C., Liao, M.H. and Wu, H.Y. (2007). Diosgenin, a steroidal sapogenin, enhances antigen-specific IgG2a and interferon-ã expression in ovalbumin-sensitized BALB/c mice. Planta Medica. October. 53(05), 421-426.

Jayachandran, K. S., Vasanthi, H. R. and Rajamanickam, G. V. (2009). Antilipoperoxidative and membrane stabilizing effect of diosgenin, in experimentally induced myocardial infarction. Molecular and Cellular Biochemistry. July 1. 327(1-2), 203-210.

Jesus, M., Martins, A. P., Gallardo, E. and Silvestre, S. (2016). Diosgenin: recent highlights on pharmacology and analytical methodology. Journal of Analytical Methods in Chemistry.

Jung, D. H., Park, H. J., Byun, H. E., Park, Y. M. , Kim, T. W., Kim, B. O., Um, S. H. and Pyo, S. (2010). Diosgenin inhibits macrophage-derived inflammatory mediators through downregulation of CK2, JNK, NF-êB and AP-1 activation. International Immunopharmacology. September 1. 10(9), 1047-1054.

Kalailingam, P., Kannanai, B., Tamilmani, E. and Kaliaperumal, R. (2014). Efficacy of natural diosgenin on cardiovascular risk, insulin secretion, and beta cells in streptozotocin (STZ)-induced diabetic rats. Phytomedicine. September 15. 21(10), 1154-1161.

Kang, T. H., Moon, E., Hong, B. N., Choi, S. Z., Son, M., Park, J. H. and Kim, S. Y. (2011). Diosgenin from Dioscorea nipponica ameliorates diabetic neuropathy by inducing nerve growth factor. Biological and Pharmaceutical Bulletin. September 1. 34(9), 1493-1498.

Kaskiw, M. J., Tassotto, M. L., Mok, M., Tokar, S. L., Pycko, R., Th'ng, J. and Jiang, Z. H. (2009). Structural analogues of diosgenyl saponins: synthesis and anticancer activity. Bioorganic & Medicinal Chemistry. November 15. 17(22), 7670-9.

Khan, H., Saeed, M., Rauf, A., Khan, M. A. and Muhammad, N. (2015). Antimicrobial and inhibition on heat-induced protein denaturation of constituents isolated from Polygonatum verticillatum rhizomes. Natural Product Research. November 17. 29(22), 2160-2163.

Kim, J. K. and Park, S.U. (2018). An update on the biological and pharmacological activities of diosgenin. EXCLI Journal. 17(24).

Kotecha, R., Takami, A. and Espinoza, J. L. (2016). Dietary phytochemicals and cancer chemoprevention: a review of the clinical evidence. Oncotarget. August 9. 7 (32), 52517.

Lee, J., Jung, K., Kim, Y. S. and Park, D. (2007). Diosgenin inhibits melanogenesis through the activation of phosphatidylinositol-3-kinase pathway (PI3K) signaling. Life Sciences. June. 81(3), 249-254.

Li, J., Liu, X., Guo, M., Liu, Y., Liu, S. and Yao, S. (2005). Electrochemical study of breast cancer cells MCF-7 and its application in evaluating the effect of diosgenin. A nalytical Sciences. 21(5), 561-564.

Malissetty, V. S., Patlolla, J. M., Raju, J., Marcus, L.A., Choi, C. I. and Rao, C. V. (2006) Chemoprevention of colon cancer by diosgenin, a steroidal sapogenin constituent of fenugreek.

Manda, V. K., Avula, B., Ali, Z., Wong, Y. H., Smillie, T. J., Khan, I. A. and Khan, S. I. (2013). Characterization of in vitro ADME properties of diosgenin and dioscin from Dioscorea villosa. Planta Medica. October. 79(15), 1421-1428.

Manivannan, J., Balamurugan, E., Silambarasan, T. and Raja, B. (2013). Diosgenin improves vascular function by increasing aortic eNOS expression, normalized dyslipidemia and ACE activity in chronic renal failure rats. Molecular and Cellular Biochemistry. December 1. 384(1-2), 113-120.
McAnuff, M. A., Harding, W. W., Omoruyi, F. O., Jacobs, H., Morrison, E. Y. and Asemota, H. N. (2005). Hypoglycemic effects of steroidal sapogenins isolated from Jamaican bitter yam, Dioscorea polygonoides. Food and Chemical Toxicology. November 1. 43(11), 1667-1672.

McAnuff, M. A., Omoruyi, F. O., Morrison, E. S. and Asemota, H. N. (2005). Changes in some liver enzymes in streptozotocin-induced diabetic rats fed sapogenin extract from bitter yam (Dioscorea polygonoides) or commercial diosgenin. West Indian Medical Journal. March. 54(2), 97-101.

Mirunalini, S. and Shahira, R. (2011). Novel effect of diosgenin—a plant derived steroid. A review. Pharmacologyonline. 1, 726-1736.

Miyoshi, N., Ishii, H., Nagano, H., Haraguchi, N., Dewi, D. L., Kano, Y., Nishikawa, S., Tanemura, M., Mimori, K., Tanaka, F. and Saito, T. (2011). Reprogramming of mouse and human cells to pluripotency using mature microRNAs. Cell Stem Cell. June 3. 8(6), 633-638.

Miyoshi, N., Nagasawa, T., Mabuchi, R., Yasui, Y., Wakabayashi, K., Tanaka, T. and Ohshima, H. (2011). Chemoprevention of azoxymethane/dextran sodium sulfate-induced mouse colon carcinogenesis by Freeze-Dried Yam Sanyaku and its constituent diosgenin. Cancer Prevention Research. June 1. 4(6), 924-934.

Naidu, P. B., Ponmurugan, P., Begum, M. S., Mohan, K., Meriga, B., Ravindar Naik, R. and Saravanan, G. (2015). Diosgenin reorganises hyperglycaemia and distorted tissue lipid profile in highfat diet-streptozotocin induced diabetic rats. Journal of the Science of Food and Agriculture. December. 95(15), 3177-3182.

Nie, C., Zhou, J., Qin, X., Shi, X., Zeng, Q., Liu, J., Yan, S. and Zhang, L. (2016). Diosgenin-induced autophagy and apoptosis in a human prostate cancer cell line. Molecular Medicine Reports. November 1. 14(5), 4349-59.

Nigam, V. (2018). Phytochemistry, anthelmintic study of herbaceous aerial part of kallstroemia pubescens (G. Don) & review of novel effects of diosgenin: a plant derived steroid. International Journal of Current Research in Physiology and Pharmacology (IJCRPP). 2(2), 5-9.

Niño, J., Jiménez, D. A., Mosquera, O. M. and Correa, Y. M. (2007). Diosgenin quantification by HPLC in a Dioscorea polygonoides tuber collection from Colombian flora. Journal of the Brazilian Chemical Society. 18(5), 1073-1076.

Patel, K., Gadewar, M., Tahilyani, V. and Patel, D.K. (2012). A review on pharmacological and analytical aspects of diosgenin: a concise report. Natural Products and Bioprospecting. April 1. 2(2), 46-52.

Pi, W. X., Feng, X. P., Ye, L. H. and Amp; Cai, B. C. (2017). Combination of Morroniside and Diosgenin Prevents High Glucose-induced Cardiomyocytes Apoptosis. Molecules. 22(1), 163.

Rababiert, J., Tiewcharoen, S., Auewarakul, P., Atithep, T., Lumlerdkij, N., Vejaratpimol, R. and Junnu, V. (2015). An anti-amebic activity of diosgenin on Naegleria fowleri trophozoites. Southeast Asian Journal of Tropical Medicine and Public Health. September 1. 46(5), 827.

Raju, J. and Mehta, R. (2008). Cancer chemopreventive and therapeutic effects of diosgenin, a food saponin. N utrition and Cancer. December 31. 61(1), 27-35.

Raju, J. and Rao, C. V. (2012). Diosgenin, a steroid saponin constituent of yams and fenugreek: emerging evidence for applications in medicine. Bioactive Compounds in Phytomedicine, IntechOpen..

Raju, J., Patlolla, J. M., Swanny, M. V. and Rao, C.V. (2004). Diosgenin, a steroid saponin of Trigonella foenum graecum (fenugreek), inhibits azoxymethane-induced aberrant crypt foci formation in F344 rats and induces apoptosis in HT-29 human colon cancer cells. Cancer Epidemiology and Prevention Biomarkers. August 1. 13(8), 1392-1398.

Sangeetha, M. K., Mal, N. S., Atmaja, K., Sali, V. K. and Vasanthi, H. R. (2013). PPAR's and diosgenin a chemico biological insight in NIDDM. Chemico-Biological Interactions. November 25. 206(2), 403-410.

Sautour, M., Mitaine-Offer, A. C., Miyamoto, T., Dongmo, A. and Lacaille-Dubois, M. A. (2004). Antifungal steroid saponins from Dioscorea cayenensis. Planta Medica. January. 70(01), 90-92.

Shen, M., Qi, C., Kuang, Y. P., Yang, Y., Lyu, Q. F., Long, H., Yan, Z. G. and Lu, Y. Y. (2017). Observation of the influences of diosgenin on aging ovarian reserve and function in a mouse model. European Journal of Medical Research. December. 22(1), 42.
Son, I. S., Kim, J. H., Sohn, H. Y., Son, K.H., Kim, J. S. and Kwon, C. S. (2007). Antioxidative and hypolipidemic effects of diosgenin, a steroidal saponin of yam (Dioscorea spp.), on high-cholesterol fed rats. Bioscience, Biotechnology, and Biochemistry. December 23. 71(12), 3063-3071.

Srinivasan, S., Koduru, S., Kumar, R., Venguswamy, G., Kyprianou, N. and Damodaran, C. (2009). Diosgenin targets Aktmediated prosurvival signaling in human breast cancer cells. International Journal of Cancer. August 15. 125(4), 961-967.

Steroids | Vol 118, Pages 1-128 (February 2017) | ScienceDirect.comhttps://www.sciencedirect.com/journal/steroids/vol/118/suppl/C

Tada, Y., Kanda, N., Haratake, A., Tobiishi, M., Uchiwa, H. and Watanabe, S. (2009). Novel effects of diosgenin on skin aging. Steroids. June 1. 74(6), 504-511.

Turchan, J., Pocernich, C. B., Gairola, C., Chauhan, A., Schifftto, G., Butterfield, D. A., Buch, S., Narayan, O., Sinai, A., Geiger, J. and Berger, J. R. (2003). Oxidative stress in HIV demented patients and protection ex vivo with novel antioxidants. Neurology. January 28. 60(2), 307-314.

Uemura, T., Goto, T., Kang, M. S., Mizoguchi, N., Hirai, S., Lee, J. Y., Nakano, Y., Shono, J., Hoshino, S., Taketani, K. and Tsuge, N. (2010). Diosgenin, the major aglycon of fenugreek, inhibits LXRα activity in HepG2 cells and decreases plasma and hepatic triglycerides in obese diabetic mice. The Journal of Nutrition. November 24. 141(1), 17-23.

Vincken, J. P., Heng, L., de Groot, A. and Gruppen, H. (2007). Saponins, classification and occurrence in the plant kingdom. Phytochemistry. February 1. 68(3), 275-297.

Wang, S., Wang, F., Yang, H., Li, R., Guo, H. and Hu, L. (2017). Diosgenin glucoside provides neuroprotection by regulating microglial M1 polarization. International Immunopharmacology. September 1. 50, 22-29.

Wang, Y. J., Liu, C., Chang, H. D., et al. (2006). Diosgenin, a plant-derived sapogenin, stimulates Ca2+-activated K+ current in human cortical HCN-1A neuronal cells [J]. Planta Med. 72(5), 430-436.

Wang, Y. J., Pan, K. L., Hsieh, T. C., Chang, T. Y., Lin, W. H. and Hsu, J. T. (2011). Diosgenin, a plant-derived sapogenin, exhibits antiviral activity in vitro against hepatitis C virus. Journal of Natural Products. March 10. 74(4), 580-584.

Wu, L., Dong, H., Zhao, J., Wang, Y., Yang, Q., Jia, C. and Ma, J. (2015). Diosgenin stimulates rat TM4 cell proliferation through activating plasma membrane translocation and transcriptional activity of estrogen receptors. Biology of Reproduction. January 1. 92(1), 24-1.

Xiao, L., Guo, D., Hu, C., Shen, W., Shan, L., Li, C., Liu, X., Yang, W., Zhang, W. and He, C. (2012). Diosgenin promotes oligodendrocyte progenitor cell differentiation through estrogen receptor mediated ERK1/2 activation to accelerate remyelination. Glia. July 1. 60(7), 1037-1052.

Yan, C. H., You-Mei, T. A., Su-Lan, Y. U., Yu-Wei, H. A., Jun-Ping, K. O., Bao-Lin Li. and Bo-Yang, Y. U. (2015). Advances in the pharmacological activities and mechanisms of diosgenin. Chinese Journal of Natural Medicines. August 1. 13(8), 578-587.

Yang, C. R., Zhang, Y., Jacob, M. R., Khan, S. I., Zhang, Y. J. and Li, X. C. (2006). Antifungal activity of C-27 steroidal saponins. Antimicrobial Agents and Chemotherapy. May 1. 50(5), 1710-1714.

Zhang, X., Xue, X., Zhao, J., Qian, C., Guo, Z., Ito, Y. and Sun, W. (2016). Diosgenin attenuates the brain injury induced by transient focal cerebral ischemia-reperfusion in rats. Steroids. September 1. 113, 103-112.

Zhou, H. T., Yu, X. F. and Zhou, G. M. (2017). Diosgenin inhibits angiotensin II-induced extracellular matrix remodeling in cardiac fibroblasts through regulating the TGF EP1/ Smad3 signaling pathway. Molecular Medicine Reports. May 1. 15(5), 2623-2628.