Diosgenin, a Steroid Saponin Constituent of Yams and Fenugreek: Emerging Evidence for Applications in Medicine

Jayadev Raju[1] and Chinthalapally V. Rao[2]
[1]Toxicology Research Division, Bureau of Chemical Safety,
Health Products and Food Branch, Health Canada,
[2]Department of Medicine, Hematology-Oncology Section,
University of Oklahoma Health Sciences Center
USA

1. Introduction

Phytochemicals found in foods and spices are progressively gaining popularity over conventional synthetic drugs mainly because they act *via* multiple molecular targets that synergize to efficiently prevent or treat chronic illnesses. Phytochemicals are also safe (with minimal or no toxic or side effects) with better bioavailability. Food saponins have been used in complimentary and traditional medicine against a variety of diseases including several cancers. Diosgenin, a naturally-occurring steroid saponin is found abundantly in legumes (*Trigonella* sp.) and yams (*Dioscorea* sp.). Diosgenin is a precursor of various synthetic steroidal drugs that are extensively used in the pharmaceutical industry. Over the past two decades, a series of pre-clinical and mechanistic studies have been independently conducted to understand the beneficial role of diosgenin against metabolic diseases (hypercholesterolemia, dyslipidemia, diabetes and obesity), inflammation and cancer. In experimental models of obesity, diosgenin decreases plasma and hepatic triglycerides and improves glucose homeostasis plausibly by promoting adipocyte differentiation and inhibiting inflammation in adipose tissues. A limited number of experiments have been conducted to understand the pre-clinical efficacy of diosgenin as a chemopreventive/therapeutic agent against cancers of several organ sites. Mechanistic studies using *in vitro* models suggest that diosgenin suppresses cancer cell growth through multiple cell signaling events associated with proliferation, differentiation, apoptosis, inflammation and oncogenesis. This chapter provides a comprehensive review of the biological activity of diosgenin that contributes to several diseases in its role as a health beneficial phytochemical by citing new studies. In addition, diosgenin's safety with regards to its potential toxicity is also critically discussed. Altogether, the findings from pre-clinical and mechanistic studies strongly implicate the use of diosgenin as a novel multi-target based chemopreventive or therapeutic agent against several chronic diseases.

1.1 Background of origin

Diosgenin is a major bioactive constituent of various edible pulses and roots, well characterized in the seeds of fenugreek (*Trigonella foenum graecum* Linn) as well as in the root tubers of wild yams (*Dioscorea villosa* Linn) (No authors listed, 2004; Taylor et al., 2000). Reference to the ethnobotanical use of fenugreek seeds appears in the Egyptian Ebers papyrus (*c.* 1500 BC) as a medicine to induce childbirth. Fenugreek seeds were referred as a "soothing herb" by the Greek physician *Hippocrates* (5th century BC) and *Dioscorides* (1st century AD) suggested its use in the treatment of gynaecological inflammation (Chevalier, 2000). Wild yam tubers on the other hand have been used traditionally as a pain reliever by the ancient *Aztec* and *Mayan* people in the Americas (Chevalier, 2000). Data available from various traditional medical practices indicate that fenugreek seeds and wild yam tubers have been purported to be used as a preventive or therapeutic medicine against several ailments including arthritis, cancer, diabetes, gastrointestinal disorders, high cholesterol, and inflammation suggesting a variety in its use (Memorial Sloan-Kettering Cancer Center).

1.2 Chemistry, structure-function and bioavailability

Structurally, diosgenin [(25*R*)-spirost-5-en-3b-ol] is a spirostanol saponin consisting of a hydrophilic sugar moiety linked to a hydrophobic steroid aglycone (Figure 1). Diosgenin is structurally similar to cholesterol and other steroids. Since its discovery, diosgenin is the single main precursor in the manufacture of synthetic steroids in the pharmaceutical industry (Djerassi et al., 1952). In a recent study it was shown that spirostanol compounds, especially diosgenin glycosides exhibited inducible or inhibitory activity in rat uterine contraction based on (a) the number, length and position of sugar side chains attached by a glycoside, and (b) related to the structure of the aglycone (Yu et al., 2010). The structure-related functions of diosgenin have been extensively tested using cancer cells *in vitro*. In comparison to two-structurally-related saponins, hecogenin and tigogenin, only diosgenin caused a cell cycle arrest associated with strong apoptosis *in vitro* (Corbiere et al., 2003).) The biological activities of diosgenin and other structurally-related steroid saponins and alkaloids were tested *in vitro* (Trouillas et al., 2005). By using molecular modelling, the spatial conformation and electron transfer capacity were calculated in relation to the structural characteristics of diosgenin necessary to elicit its effect on proliferation rate, cell cycle distribution and apoptosis; and the anti-cancer bioactivity of diosgenin was shown to be related to the presence of a hetero-sugar moiety and the 5,6-double bond in its structure (Trouillas et al., 2005). Moreover, structural conformation at C-5 and C-25 carbon atoms was shown to be important for diosgenin's biological activity (Trouillas et al., 2005). Further studies are warranted to assess the structure-function relationship of diosgenin and to understand whether and how synthetic changes brought about could augment its biological activity in favour of its role as a therapeutic agent. Rodent studies on the disposition of diosgenin revealed that diosgenin was poorly absorbed and underwent extreme biotransformation (Cayen et al., 1979). In the same study, 1 µg/mL of diosgenin was recovered from the serum of human subjects receiving an oral dose of 3 g diosgenin per day for 4 weeks suggesting poor absorption and possibly active biotranformation (Cayen et al., 1979).
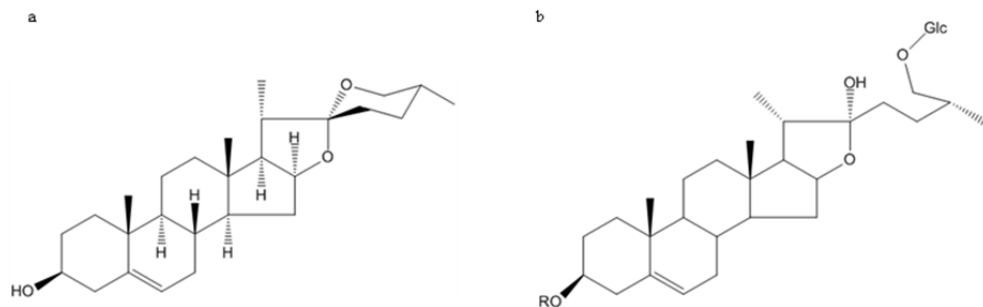
Fig. 1. Structure of diosgenin: Diosgenin (a) and its analogue protodioscin (b) are steroid saponins consisting of a hydrophilic sugar moiety linked to a hydrophobic steroid aglycone

2. Metabolic diseases

Fenugreek seeds and *Dioscorea* sp. yam tubers together with their constituent diosgenin have been shown to have biological activity against several metabolic diseases (Ulbricht et al., 2007; Raju & Rao, 2009). In the following sections, studies that have used the active constituent diosgenin in both experimental models of metabolic diseases and human clinical studies are reviewed. A list of studies evaluating the effects of diosgenin against different metabolic diseases is summarised in Table 1.

Disease/ Effect	Experimental model	Benificial potency Yes (Y) or No (N)	References
Dyslipidemia/obesity Cholesterol-lowering	Cholesterol-fed rats	Y	Cayen and Dvornik, 1979 Juarez-Oropeza et al., 1987 Son et al., 2007
	Cholesterol-fed chickens	Y	Cayen and Dvornik, 1979
	Cholesterol-fed rabbits	Y	Cayen and Dvornik, 1979
Adipocyte-differentiation/ inflammation	Normal rats	N	Cayen and Dvornik, 1979
	3T3-L1 (Mouse embryonic fibroblast - adipose like cells)	Y	Uemura et al., 2010
Diabetes Blood glucose	Streptozotocin-induced diabetic rats	Y	McAnuff et al., 2005
Liver function Cholestasis	FVB mice	Y	Kosters et al., 2005
	Wistar rats	Y	Nibbering et al., 2001 Nervi et al., 1998
	NPC1L1-knockout (L1KO) and wild-type mice	Y	Temel et al., 2009

Table 1. Effect of diosgenin (purified) on metabolic and related diseases

2.1 Dyslipidemia and obesity

The lipid-lowering potential of diosgenin has been demonstrated by several experimental studies (Sauvaire et al., 2000). Diosgenin decreased the elevated cholesterol in serum LDL and HDL fractions in cholesterol-fed rats, and had no effect on serum cholesterol in normocholesterolemic rats. In addition, diosgenin inhibited cholesterol absorption, and suppressed its uptake in serum and liver, and its accumulation in the liver (Cayen and Dvornik, 1979). Diosgenin lowered plasma cholesterol in diet-induced hypercholesterolemic rats, chicken and rabbits when administered orally or parenterally (Juarez-Oropeza et al., 1987). Recently, it was shown that diosgenin (at a oral dose of 0.1% or 0.5% in the diet for 6 weeks) decreased total cholesterol levels and increased the plasma high-density lipoprotein (HDL) cholesterol level in both plasma and livers of diet-induced hypercholesterolemic rats (Son et al., 2007). In a study that evaluated the anti-obesity role of diosgenin-rich *Dioscorea nipponica* Makino, a related species to *Dioscorea villosa*, Sprague-Dawley rats fed a diet containing 40% beef tallow and 5% freeze-dried extract of the yam gained less body weight and adipose tissue than those that received only the 40% beef tallow diet (Kwon et al., 2003). In the same study it was shown that diosgenin suppressed the time-dependent increase of blood triacylglycerol levels when orally administered with corn oil to ICR mice, suggesting an inhibitory potential against fat absorption (Kwon et al., 2003).

An evidence-based systemic review clearly suggests that fenugreek seeds (rich in diosgenin content) have an important role in the control of metabolic diseases such as diabetes and obesity (Ulbricht et al., 2007). Fenugreek decreased the size of adipocytes in diabetic obese KK-Ay mice suggesting an increased differentiation of adipocytes leading to decreased adipocyte lipid accumulation (Uemura et al., 2010). These results were further validated with molecular data that showed that fenugreek increased the mRNA expression levels of differentiation-related genes in adipose tissues (Uemura et al., 2010). Furthermore, *in vitro* experiments using 3T3-L1 adipocytes showed that diosgenin, the major saponin in fenugreek, promoted 3T3-L1 adipocyte differentiation to enhance insulin-dependent glucose uptake (Uemura et al., 2010). Two clinical studies were recently published showing the anti-obesity properties of fenugreek seeds. First, a double-blind randomized placebo-controlled three-period (14 days) cross-over trial with twelve healthy male volunteers, demonstrated that fenugreek seed extract selectively reduced spontaneous fat consumption compared to placebo controls (Chevassus et al., 2009). However, there was no effect on body weight, normal and fasting glucose levels, insulin and lipid profile, and visual analogue scale scores of appetite/satiety in subjects receiving the fenugreek seed extract (Chevassus et al., 2009). In the second study, a 6-week double-blind randomized placebo-controlled parallel trial with thirty-nine healthy overweight male volunteers, showed decreased dietary fat consumption in subjects that received a fixed dose of a fenugreek seed extract compared to those that received the placebo (Chevassus et al., 2010). In addition, subjects that received the fenugreek seed extract also demonstrated a decrease in the insulin/glucose ratio in the serum of fasted subjects (Chevassus et al., 2010). Put together, these two clinical studies provided evidence to support that fenugreek seeds may potentially regulate fat consumption in humans. Whether diosgenin *per se* can mimic these results at appreciable doses in human subjects need to be addressed.

2.2 Diabetes

There are several reports suggesting that diosgenin-rich food sources such as fenugreek seeds and yam tubers contribute to anti-diabetic effects in experimental models (Basch et al., 2003; Omoruyi, 2008). Evidence from human clinical trials clearly suggests that fenugreek seeds improve blood glucose and other metabolic parameters leading to treatment of diabetes (Basch et al., 2003).) Diosgenin significantly decreased plasma glucose in streptozotocin-induced diabetic rats by comparison to the diabetic controls suggesting its anti-diabetic properties (McAnuff et al., 2005). These results were further strengthened by the fact that several hepatic rate-limiting enzymes commonly involved in glucose metabolism altered in the diabetic state were normalized by treatment with diosgenin (McAnuff et al., 2005). While there is ample evidence (including clinical trials) suggesting that fenugreek seeds may be used as an alternative medicine to treat diabetes and associated complications, more experimental studies are warranted to address if diosgenin can be efficaciously used in the control of diabetes and to understand the mechanism(s) of action.

2.3 Liver function, liver disease and bile secretion

There is a plethora of information that suggests that both fenugreek seeds and yam tubers influence several metabolic diseases directly affecting a number of molecular targets involved in enzyme metabolism as well as signal transduction pathways in the liver suggesting that their active compounds such as diosgenin may plausibly modulate liver function and may aid in the therapeutic control of liver diseases. A lyophilized fraction of *Dioscorea* sp. yam tubers attenuated CCl_4-induced hepatic fibrosis in rats in a dose-dependent manner (Chan et al., 2010). On the other hand, aqueous extract of fenugreek seeds contributed to a significant histopathological protection against ethanol-induced liver toxicity in rats (Thirunavukkarasu et al., 2003). Furthermore, the authors reported that this protection against ethanol-induced toxicity was by modulating lipid peroxidation and the antioxidant status (Thirunavukkarasu et al., 2003). Powdered fenugreek seeds administered in the diet at a dose of 5% (wt/wt) reduced the liver weight and alleviated hepatic steatosis in Zucker obese (*fa/fa*) rats (Raju and Bird, 2006). The main mechanism of fenugreek seeds in controlling hepatic steatosis was through lowering plasma tumor necrosis factor (TNF)-α, a proinflammatory cytokine and by decreasing total fat and triglycerides in the liver (Raju and Bird, 2006). Specifically, there are no reports demonstrating the therapeutic potency of diosgenin against liver disease. It is postulated that diosgenin feeding causes cholesterol excretion in the stool of experimental animals, mainly by cholesterol secretion from the bile (Cayen and Dvornik, 1979). Diosgenin has been shown to increase cholesterol secretion five- to seven-fold in the bile of rats without altering the output of bile salts and phospholipids (Kosters et al., 2005; Nervi et al., 1988; Nibbering et al., 2001). Recently, it was shown that the bilary cholesterol secretion stimulated by diosgenin and leading to fecal cholesterol excretion is independent of intestinal cholesterol absorption (Temel et al., 2009).

3. Cancer

3.1 *In vivo* studies

There are limited experimental studies addressing the *in vivo* tumor modulating potential of diosgenin (summarised in Table 2). Diosgenin inhibited the formation of colon aberrant crypt foci (ACF), putative precancerous lesions induced by azoxymethane (AOM) in F344

rats. In this study, administration of diosgenin in the diet at a dose of 0.1% and 0.05% (wt/wt) either during initiation/post-initiation or promotion stages significantly suppressed AOM-induced colon ACF (Raju et al., 2004). The demonstrated ability of diosgenin to inhibit both the total number of ACF and large ACF (those with crypt multiplicity of four or more) suggests that it could effectively prevent, retard and cease the appearance and growth of precancerous lesions in the colon (Raju et al., 2004). Furthermore the lower dose of 0.05% was as effective as the higher dose of 0.1% in blocking ACF formation (Raju et al., 2004). In a double-blind study designed to assess the tumor-modulating potential of diosgenin using the AOM-injected F344 rats, Malisetty et al. (2005) reported that 0.1% of diosgenin suppressed the incidence of both invasive and non-invasive colon adenocarcinomas by up to 60% (Malisetty et al., 2005). In addition, diosgenin decreased colon tumor multiplicity (adenocarcinomas/rat) compared to Controls. In part, these *in vivo* effects were shown to be related to a lower proliferating cell nuclear antigen (PCNA) index in colon tumors suggesting that diosgenin attenuates tumor cell proliferation (Malisetty et al., 2005).

Organ site Pathological target	Experimental model	Inhibition* Yes (Y) or No (N)	References
Colon			
Aberrant crypt foci	AOM-induced rats	Y	Raju et al., 2004
Tumors	AOM-induced rats	Y	Malisetty et al., 2005
Ulcers/tumors	AOM/DSS-induced ICR mice	Y	Miyoshi et al., 2011
Breast			
MCF-7 tumor xenografts	Nude (*nu/nu*) mice	Y	Srinivasan et al., 2009
MDA 231 tumor xenografts	Nude (*nu/nu*) mice	Y	Srinivasan et al., 2009
Lung			
LA795 ectopic tumors	T739 mice	Y	Yan et al., 2009

*Inhibition of either (a) tumor incidence [number of tumor-bearing animals], (b) tumor multiplicity [number of tumors per tumor-bearing rats], or (c) tumor size.

Table 2. *In vivo* anticancer effects of diosgenin (purified)

Diosgenin has been shown to attenuate inflammatory process in relevant animal models. For instance, diosgenin dose-dependently attenuated sub-acute intestinal inflammation and normalized bile secretion in indomethacin-induced intestinal inflammation in rats (Yamada et al., 1997). The role of chronic inflammation on carcinogenesis is vital (Dinarello, 2006); thus the study by Yamada et al. (1997) demonstrating the ability of diosgenin to effectively treat inflammation could be extrapolated to its prospective chemopreventive action against cancers. Recently, the efficacy of diosgenin against AOM/dextran sodium sulphate (DSS)-induced inflammation-associated colon carcinogenesis in ICR mice was reported (Miyoshi N et al., 2011). Diosgenin at doses of 20, 100 and 500 mg/kg (wt/wt) in the diet reduced AOM/DSS induced ulcers to 53%, 46% and 40%, respectively in comparison to control (Miyoshi et al, 2011). While diosgenin did not alter the incidence of colon tumors (adenoma + adenocarcinoma), it reduced the tumor multiplicity significantly at all the three tested doses (Miyoshi N et al., 2011). Furthermore, it was shown that diosgenin's potency against

experimentally-induced inflammation-associated colon carcinogenesis was in part mediated by the alteration of lipid metabolism (reduced serum triglyceride levels by up-regulation of lipoprotein lipase), and the modulation of genes associated with inflammation and multiple signaling pathways (Miyoshi N et al., 2011).

With regards to breast cancer, the effect of diosgenin on the ectopic growth of human breast cancer MCF-7 and MDA 231 tumor xenografts was studied in nude mice (Srinivasan et al., 2009). It was reported that diosgenin (10 mg/kg body weight administered intra-tumorally) significantly inhibited the growth of tumor xenografts of both MCF-7 and MDA 231 compared to vehicle-treated controls, with no toxicity to any of the vital organs in the experimental mice (Srinivasan et al., 2009). To test the anti-aging properties of diosgenin in relation to hormonal-effects *in vivo*, Tada et al. (2009) assessed the effect of diosgenin-rich *Dioscorea* Sp. yam tuber extract on the ectopic growth of estradiol-dependent human breast cancer (MCF-7) in ovarectomized nude mice for 12 weeks. Diosgenin containing extracts was shown to repress the size of the tumors compared to sham controls (Tada et al., 2009). Yan et al. (2009) reported that oral administration of diosgenin at a dose of 200 ppm (p.o.) significantly inhibited the growth mouse LA795 lung adenocarcinoma tumors by 33.94% in T739 inbred mice.

3.2 *In vitro* studies

The anti-cancer effects of diosgenin *in vitro* through different mechanisms are discussed in the following sub-sections. Many molecular candidates critical to tumorigenesis are affected by diosgenin (Raju and Mehta, 2009; Raju and Rao, 2009). The *in vitro* anticancer effects of diosgenin and its cellular/molecular effects is summarised in Table 3.

3.2.1 Colon cancer

Diosgenin inhibited the growth of HT-29 and HCT-116 human colon adenocarcinoma cells (Lepage et al., 2010; Raju and Bird, 2007; Raju et al., 2004). Diosgenin induced apoptosis in HT-29 cells, in part by inhibition of bcl-2 and by induction of caspase-3 protein expression (Raju et al., 2004). Lepage et al. (2010) reported that in HT-29 cells, diosgenin at 40 µM caused delayed apoptosis together with an increase in cyclooxygenase (COX)-2 expression and activity, higher 5-lipooxygenase (LOX) expression and enhanced leukotriene B4 production. COX-2 inhibition by NS-398 strongly sensitized HT-29 cells to diosgenin-induced apoptosis (Lepage et al., 2010). Furthermore, diosgenin was shown to sensitize HT-29 cells to TRAIL-induced apoptosis (Lepage et al., 2011). In HCT-116 cells, diosgenin was shown to induce apoptosis by the cleavage of the 116 kDa poly (ADP-ribose) polymerase (PARP) protein to the 85kDa fragment (Raju and Bird, 2007). In addition, it was shown that diosgenin significantly lowered the expression of HMG-CoA reductase at both mRNA and protein levels, suggesting the involvement of the cholesterol biosynthetic pathway in diosgenin's efficacy as an anti-cancer agent (Raju and Bird, 2007).

3.2.2 Breast cancer

Diosgenin arrested the growth of HER2 oncoprotein-overexpressing AU565 human breast adenocarcinoma cells at sub-G_1 phase (Chiang et al., 2007). Selective apoptosis induced by diosgenin in these cells was found to be through PARP cleavage involving the down-

Organ site	Cancer cell type	Cellular/molecular targets	References
Colon	HT-29	Apoptosis/ bcl-2, caspase-3, COX-2, 5-LOX	Raju et al., 2004 Lepage et al., 2010; 2011
	HCT-116	Apoptosis/ PARP, COX-2, 5-LOX Lipid metabolism/ HMG-CoA reductase	Raju et al., 2007 Lepage et al., 2010; 2011 Raju et al., 2007
Breast	AU565	Apoptosis/ PARP, mTOR, JNK Lipid metabolism/FAS	Chiang et al., 2007
	MCF-7	Growth-proliferation/ Akt, p53 Apoptosis/ NF-κB, Bcl-2, survivin	Srinivasan et al., 2009
	MDA 231	Growth-proliferation/ ERK Apoptosis/caspase-3, NF-κB, Bcl-2, survivin	Srinivasan et al., 2009
Prostate	PC-3	Growth-proliferation/ PI3K, Akt, ERK, JNK, NF-κB Angiogenesis/ VEGF	Chen et al., 2011
	DU145	Growth-invasion/ HGF, mdm2, vimentin, Akt, mTOR	Chang et al., 2011
Cervix	CaSki	Growth-proliferation	Fernández-Herrera et al., 2010
Liver	HCC	Apoptosis/caspase-3, PARP Transcription/ STAT3, cSrc	Li et al., 2010
Bone/blood	1547 osteosarcoma	Apoptosis/ NF-κB, p53, PPAR-γ, COX-2	Corbiere et al., 2003; 2004a Moalic et al., 2001
	RAW-264.7	Growth-proliferation/ NF-κB, RANK-L	Shishodia and Aggarwal, 2006
	KBM-5	Growth-proliferation/ NF-κB, IκBα, cyclin-D1,	Shishodia and Aggarwal, 2006
	HEL	Apoptosis/ PARP, caspase-3, p21 Eicosanoid biosynthesis/ COX-2, 5-LOX/cPLA2	Leger et al., 2004a; 2006 Leger et al., 2004b; Napez et al., 1995
	K562	Apoptosis/ PARP, caspase-3, NF-κB, COX-2, p38 MAPK	Liagre et al., 2005
Larynx	HEp-2	Apoptosis/ p53	Corbiere et al., 2004b
Skin	M4Beu	Apoptosis/ p53	Corbiere et al., 2004b

Table 3. *In vitro* anticancer activities of diosgenin (purified)

regulation of phospho-Akt and phospho- mammalian target of rapamycin (mTOR), and up-regulation of phospho- c-Jun N-terminal kinase (JNK) independent of p38 and extracellular signal regulating kinase (ERK) phosphorylations (Chiang et al., 2007). In the same cell-line (AU565 cells), diosgenin inhibited the expression of fatty acid synthase (Chiang et al., 2007). The anti-cancer mechanism of diosgenin was shown to be different in human breast cancer cells based on the status of estrogen receptor (ER) expression (Srinivasan et al., 2009). In ER-positive MCF-7 human breast cancer cells, diosgenin induced p53 tumor suppressor protein; while the pro-apoptotic mechanism of diosgenin in ER-negative MDA human breast carcinoma cells involved the activation of caspase-3 and down-regulation of bcl-2 (Srinivasan et al., 2009).

3.2.3 Prostate cancer

Diosgenin inhibited proliferation of PC-3 human prostate cancer cells in a dose-dependent manner (Chen et al., 2011). At non-toxic doses, diosgenin suppressed cell migration and invasion by reducing the activities and mRNA expression of matrix metalloproteinase (MMP) -2 and MMP-9 (Chen et al., 2011). Diosgenin abolished the expression of vascular endothelial growth factor (VEGF) in PC-3 cells and tube formation of endothelial cells (Chen et al., 2011). In addition, diosgenin downregulated the phosphorylation of phosphatidylinositide-3 kinase (PI3K), Akt, ERK and JNK proteins and significantly decreased the nuclear level of nuclear factor (NF)-κB, suggesting that diosgenin inhibited NF-κB activity (Chen et al., 2011). Another study using DU145 human prostate cancer cells found that diosgenin abrogated hepatocyte growth factor (HGF)-induced cell scattering and invasion, together with inhibition of Mdm2 and vimentin through down-regulation of phosphorylated Akt and mTOR (Chang et al., 2011).

3.2.4 Cervical cancer

Recently, Fernández-Herrera et al. (2010) reported the synthesis of a novel 26-hydroxy-22-oxocholestanic steroid from diosgenin and its anticancer activity against human cervical cancer CaSki cells. Mainly this diosgenin-derivative caused apoptosis at non-cytotoxic doses activation of caspase-3 along. Furthermore, they report that antiproliferative doses of this compound observed in cancer cells did not affect the proliferative potential of normal fibroblasts from cervix and peripheral blood lymphocytes (Fernández-Herrera et al., 2010).

3.2.5 Liver cancer

Diosgenin was shown to inhibit the proliferation of hepatocellular carcinoma (HCC) cells in a dose and time-dependent manner (Liu et al., 2005). Diosgenin caused arrest of HCC cells at the G_1 phase of the cell cycle and induced apoptosis through caspase-3 activation leading to PARP cleavage (Li et al., 2010). In these cells, diosgenin inhibited both constitutive and inducible activation of signal transducers and activators of transcription (STAT)3 with no effect on STAT5, and suppressed the activation of c-Src, Janus-family tyrosine kinases (JAK)1 and JAK2 implicated in STAT3 activation (Li et al., 2010).

3.2.6 Other cancers

Cytotoxic effects of diosgenin were reported in human cancer cell lines of various other organ types: osteosarcoma (Corbiere et al., 2003, Moalic et al., 2001), leukemia (Liu et al.,

2005) and erythroleukemia (Leger et al., 2004a). The growth of 1547 human osteosarcoma cells was inhibited through G_1 phase cell cycle arrest and induction of apoptotic demise; and the main the mechanism involved the activation of p53 and binding of NFκB to DNA independent of PPAR-γ (Corbiere et al., 2003, 2004a). Interestingly, diosgenin's effect in suppressing osteoclastogenesis in RAW-264.7 cells was reported to follow a pro-apoptotic mechanism through receptor activated NFκB ligand (RANK-L) induction (Shishodia and Aggarwal, 2006). Moalic et al. (2001) demonstrated that diosgenin inhibited COX-2 activity and expression in human osteosarcoma 1547 cells.

Diosgenin arrested chronic myelogenous leukemia KBM-5 cells of human origin at sub-G_1 phase of cell cycle arrest (Shishodia and Aggarwal, 2006). This cell cycle arrest was correlated to the inhibition of tumor necrosis factor (TNF)-dependent NF-κB activation and TNF-induced degradation and phosphorylation of IκBα (the inhibitory subunit of NF-κB) (Shishodia and Aggarwal, 2006). Diosgenin downregulated TNF-induced cyclin D1 in KBM-5 cells (Shishodia and Aggarwal, 2006). Furthermore it abolished both basal and TNF-induced COX-2 gene products in a time-dependent manner (Shishodia and Aggarwal, 2006). Diosgenin controlled the growth of human erythroleukemia TIB-180 (HEL) cells by arresting cells at G_2/M cell cycle and inducing apoptosis through PARP cleavage, activation of caspase-3 and up-regulation of p53-independent p21 (Leger et al., 2004a, 2004b, 2006). Diosgenin treatment to HEL cells induced cytosolic phospholipase (cPL)A2 activation through translocation to the cellular membrane together with an increase in COX-2 expression (Leger 2004b). In a study by Nappez et al. (1995), it was reported that diosgenin treatment in HEL cells did not affect 5-LOX mRNA or 5-LOX activating protein (FLAP) mRNA at the transcriptional level. However, when HEL cells undergoing differentiation were incubated with diosgenin in the presence of indomethacin (a COX inhibitor), the growth inhibitory effect of diosgenin was reversed and an exponential growth kinetic of undifferentiated cells was observed (Nappez et al., 1995). Taken together, these studies provide an insight into the role of 5-LOX in diosgenin's modulation of growth and differentiation in HEL cells. Leger et al. (2004b) demonstrated that diosgenin increased the synthesis of arachidonic acid in HEL cells leading to COX-2 overexpression, which was accompanied by apoptosis induction. The anticancer activity of diosgenin was also shown in human erythroleukemia K562 cells through caspase-3-activation dependent PARP-mediated pro-apoptotic effects (Liagre et al., 2005). Diosgenin induced COX-2-independent apoptosis through activation of the p38 MAP kinase signalling pathway and inhibition of NFκB binding in COX-2 deficient K562 cells (Liagre et al., 2005). The anticancer mechanism of diosgenin was also shown in laryngocarcinoma HEp-2 and melanoma M4Beu cells through a p53-dependent cell death meachnism (Corbiere et al., 2004b).

4. Other diseases and ailments

A clinical study by Turchan-Cholewo et al. (2006) reported that diosgenin may have therapeutic potential against an increased risk of developing dementia in opiate abusers with HIV infection. Recently, the effect of diosgenin on hepatitis C virus (HCV) replication was reported (Wang et al., 2011). Based on a reporter-based HCV subgenomic replicon system, diosgenin was found to inhibit HCV replication at low μM concentrations *in vitro* (Wang et al., 2011). Furthermore, a combination of diosgenin and interferon-α exerted an additive effect on the resultant anti-HCV activity (Wang et al., 2011). The neuroprotective

effect of diosgenin against d-galactose-induced senescence in mice by improving cognitive abilities as assessed through the Morris water maze test and mediated by enhancing endogenous antioxidant enzyme activities (Chiu et al., 2011). Diosgenin induced apoptosis in non-cancerous human rheumatoid arthritis synoviocytes (RAS) through the overexpression of COX-2 protein and concomitant increase in the level of prostaglandin (PG)-E_2 (Liagre et al., 2004, 2007). Diosgenin may be an effective inhibitor of hyperpigmentation, commonly seen in skin disorders and inhibits melanogenesis by activating the PI3K pathway and (Lee et al., 2007). A novel effect of diosgenin in restoration of keratinocyte proliferation in aged skin in an animal model suggests that diosgenin may have a potential in slowing the aging process in the skin commonly associated with climacteric (Tada et al., 2009). Recent data support the possibility that some diosgenin-glycoside derivatives may represent a new type of contractile agonist for the uterus and their synergism may be responsible for their therapeutic effect against abnormal uterine bleeding (Yu et al., 2010).

5. Safety

There is a claim that diosgenin has an endocrine effect (estrogen-like or progesterone-like activity) in humans, however there is no scientific evidence to its validation (Djerassi et al., 1952; No authors listed, 2004). Diosgenin is neither synthesized nor metabolically converted into steroid by-products in the mammalian body. Toxicology studies using relevant experimental models have established that even at an upper concentration of 3.5% (wt/wt), diosgenin was safe and failed to cause systemic toxicity, genotoxicity, or estrogenic activity (63). Qin et al. (2009) reported that ethanol extracts of *Dioscorea* sp. containing 28.34% (wt/wt of lyophilized powder) did not cause any signs of acute toxicity in mice at an upper tested dose of 562.5 mg/kg/d, and did not significantly change toxicological parameters up to a dose of 255 mg/kg/d. No acute renal or hepatic toxicity associated with the administration of extracts of *Dioscorea villosa* at an oral dose of 0.79 g/kg/d (Wojcikowski et al., 2008). However, an increase in fibrosis in the kidneys and in inflammation in livers when rats were on the dose for 28 days was reported in the same study (Wojcikowski et al., 2008). Thus it was concluded that these toxicology effects be considered when consuming these extracts on a long-term basis, especially in people with compromised renal or hepatic function (Wojcikowski et al., 2008). On the other hand, in a 90-day subchronic study, rats fed fenugreek seeds, at doses between 1% and 10% in pure diet, had no toxic effects (Muralidhara et al., 1999). Typically, fenugreek seeds are known to contain ~0.42% to 0.75% diosgenin depending on the cultivars and seed quality (Taylor et al., 2000). Fenugreek seed extract evaluated using the standard battery of tests (reverse mutation assay, mouse lymphoma forward mutation assay and mouse micronucleus assay) recommended by US Food and Drug Administration (FDA) for food ingredients came negative and thus rendered safe for consumption at the therapeutic doses tested (Flammang et al., 2004). A recent study using human sera indicated that fenugreek seed powder contains several proteins that potentially act as allergens (Faeste et al., 2009); however, it remains unclear if diosgenin in interaction with any proteins would test positive in these allergen tests. More studies are warranted to understand the toxicological effects of diosgenin at both levels present in common foods as well as therapeutic doses. Although there is toxicology data with regards to diosgenin-rich botanicals such as *Dioscorea* sp. yam tubers and fenugreek seeds, there is a clear lack of data studying the safety of diosgenin *per se*. Some of the important aspects for

future studies assessing the toxicology of diosgenin include those related to developmental toxicity, neurotoxicity and allergenicity.

6. Conclusions

With changing lifestyle patterns such as diet and physical activity combined with factors such as genetic predispositions and smoking, the incidences of metabolic diseases including diabetes and obesity and certain kinds of cancers are increasing worldwide and hence are a public health concern with major economic impacts. While the pathogenesis of these diseases is different, there appears to be one or more molecular candidates that are commonly up- or down-regulated leading to the notion that these could be common molecular targets in prevention or therapeutic interventions of diseases. Ethnomedicine has been instrumental in providing important clues as to the role herbs and foods and their bioactive constituents in disease prevention and therapy; however, rigorous experimental-based evidence in support of ethnomedicine-derived notions would lead to the development of products relevant to and drug development. Several naturally-occurring compounds such as those in edible plants or spices are known to target multiple molecular pathways of signalling, thus bestowing them a broad preventive/therapeutic potential against several diseases. For example, curcumin from turmeric, resveratrol from grapes and epigallocatechin gallate (EGCG) from green tea have shown excellent pre-clinical potency against a wide range of diseases (reviewed in Epstein et al., 2010; Marques et al., 2009; Saito et al., 2009). These natural compounds have also been tested in clinical trials as potential therapeutics against several diseases. One emerging natural compound of interest with similar potency as curcumin, resveratrol and EGCG is diosgenin. In the above sub-sections, we have discussed in detail, the health promoting effects of diosgenin and diosgenin-rich
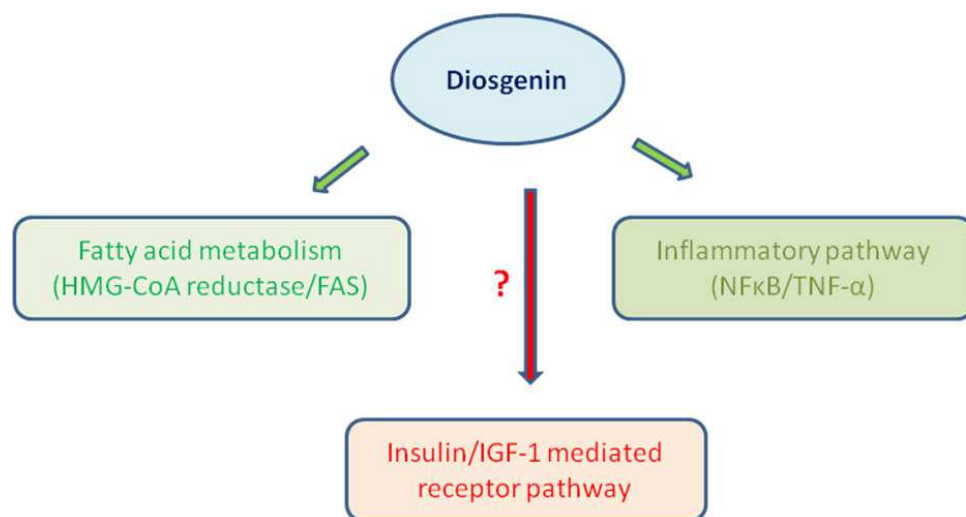
Fig. 2. Schematic representation depicting the molecularmode of action of diosgenin in the control of metabolic pathway. Diosgenin plausibly regulates signaling molecules in fatty acid metabolism and inflammatory pathway. Insulin and IGF-1 mediated signalling pathways may also be regulated by diosgenin and are thus candidates for future studies

sources: (a) *Dioscorea* sp. yam tubers and (b) *Trigonella* sp. (fenugreek) seeds. In addition, we have summarised the toxicology data pertaining to the safe use of diosgenin either in a pure form (where data was available) or in extracts. The health promoting effects of diosgenin can be broadly divided according to the differential molecular mechanisms it elicits. First, there is a growing body of experimental evidence suggesting the use of diosgenin in the treatment of metabolic diseases. Much of this is rendered through diosgenin's capacity to lower lipids in the blood and perhaps in tissues such as liver and adipose tissue. To date, there is some evidence that implicates both inflammatory pathway-associated NFκB and fatty acid metabolism-associated HMG-CoA reductase and FAS as potential molecular targets of diosgenin (Chiang et al., 2007; Raju and Bird, 2007), and these may be extended to its role as a therapeutic against metabolic diseases (Figure 2). Pathways associated with insulin and insulin-like growth factor (IGF)-1 may be of relevance in understanding the molecular mechanism of diosgenin's action in the control of metabolic diseases (Figure 2). Second, the role of diosgenin in modulating cancers has been substantially addressed; most of these data are related to the growth and proliferation of human cancer cell types and its potential mechanism(s) of action *in vitro*. Several molecular candidates associated with fatty acid metabolism (Chiang et al., 2007; Raju and Bird, 2007), inflammatory pathway (Leger et al., 2006; Liagre et al., 2005; Shishodia and Aggarwal, 2006), eicosanoid biosynthesis (Leger et al., 2004; Lepage et al., 2010; 2011; Moalic et al., 2001; Napez et al., 1995), cell proliferation and growth (Chiang et al., 2007; Leger et al., 2006; Srinivasan et al., 2009), apoptosis (Corbiere et al., 2004; Leger et al., 2006; Lepage et al., 2010; 2011; Raju and Bird, 2007; Raju et al., 2004), and regulation of transcription (Chiang et al., 2007; Li et al., 2010) are affected (up- or down-regulated) by diosgenin leading to tumor cell death (Figure 3).
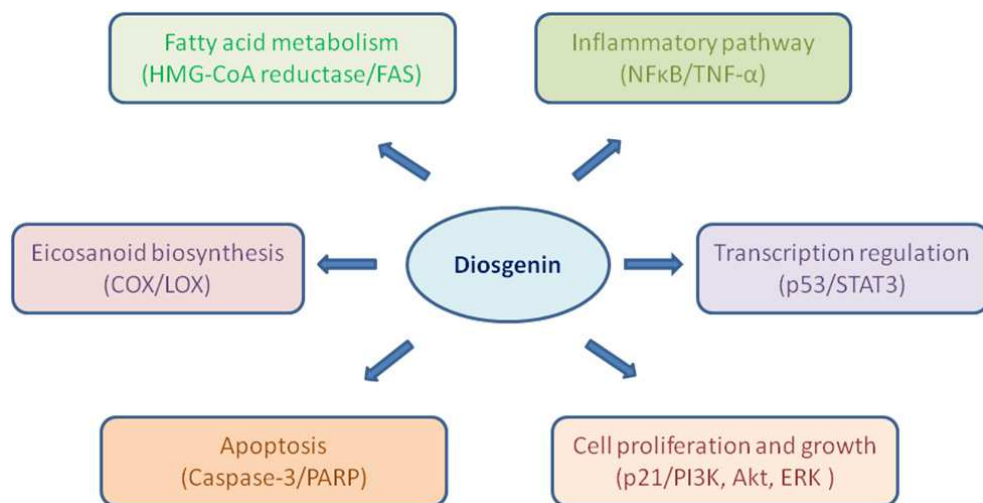

Fig. 3. Schematic representation of plausible mechanism of action(s) of diosgenin at the cellular level as a cancer chemopreventivel/therapeutic agent. Diosgenin up- or down-regulates several molecular candidates associated with cell proliferation and growth, apoptosis, regulation of transcription, fatty acid metabolism, inflammatory pathway and eicosanoid biosynthesis leading to tumor cell death.

While there are ample *in vivo* studies available to implicate the beneficial effects of diosgenin against metabolic disease, more studies to understand the specific modes of action at the molecular level are warranted. On the contrary, substantial *in vitro* evidence exists to understand the molecular mechanism of action of diosgenin against several cancers. More *in vivo* studies are thus essential to understand the physiological relevance of such data in controlling cancers. Moreover, there is excellent opportunity to address whether diosgenin plays a role in chemoprevention versus therapy, or both, in cancers of various organ sites using relevant models. The health beneficial effects of diosgenin are further extended to its potential role to treat other ailments such as HIV and hepatitis-C infections as well as liver diseases. There is little information regarding the bioavailability, pharmacokinetics and pharmacodynamics of diosgenin in relation to its health beneficial effects. Diosgenin and diosgenin-containing products are emerging in the market and are being promoted as natural health products. The scientific knowledge in this area is limited and hence extensive pre-clinical and clinical research should be carried out prior to advocating the safe and efficacious use of diosgenin and diosgenin-rich plant extracts against the prevention and control of diseases. Furthermore, such research will assist in the development of evidence-based regulation of diosgenin and disogenin-containing products as they become increasingly popular and enter the market.

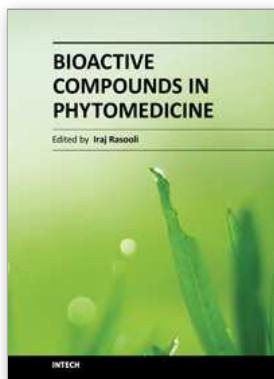## 7. Grant information

8. Acknowledgements

9. References

Basch E, Ulbricht C, Kuo G, Szapary P & Smith M. (2003). Therapeutic applications of fenugreek. Altern Med Rev. 8(1): 20-27.

Cayen MN, & Dvornik D. (1979). Effect of diosgenin on lipid metabolism in rats. J Lipid Res. 20: 162–174.

Cayen MN, Ferdinandi ES, Greselin E, & Dvornik D. (1979). Studies on the disposition of diosgenin in rats, dogs, monkeys and man. Atherosclerosis 33: 71-87.

Chan YC, Chang SC, Liu SY, Yang HL, Hseu YC, & Liao JW. (2010) Beneficial effects of yam on carbon tetrachloride-induced hepatic fibrosis in rats. J Sci Food Agric. 90(1): 161-167.

Chang HY, Kao MC, Way TD, Ho CT, & Fu E. (2011) Diosgenin suppresses hepatocyte growth factor (HGF)-induced epithelial-mesenchymal transition by down-regulation of Mdm2 and vimentin. J Agric Food Chem. 59(10): 5357-5363.

Chen PS, Shih YW, Huang HC, & HW. (2011) Diosgenin, a Steroidal Saponin, Inhibits Migration and Invasion of Human Prostate Cancer PC-3 Cells by Reducing Matrix Metalloproteinases Expression. PLoS One. 6(5): e20164.

Chevallier A. (2000) The encyclopedia of herbal medicine. 2nd edition Dorling Kindersley, Ltd. London.

Chevassus H, Molinier N, Costa F, Galtier F, Renard E, & Petit P. (2009) A fenugreek seed extract selectively reduces spontaneous fat consumption in healthy volunteers. Eur J Clin Pharmacol. 65(12): 1175-1178.

Chevassus H, Gaillard JB, Farret A, Costa F, Gabillaud I, Mas E, Dupuy AM, Michel F, Cantié C, Renard E, Galtier F, & Petit P. (2010) A fenugreek seed extract selectively reduces spontaneous fat intake in overweight subjects. Eur J Clin Pharmacol. 66(5): 449-455.

Chiang CT, Way TD, Tsai SJ, & Lin JK. (2007) Diosgenin, a naturally occurring steroid, suppresses fatty acid synthase expression in HER2-overexpressing breast cancer cells through modulating Akt, mTOR and JNK phosphorylation. FEBS Lett. 581(30): 5735-5742.

Corbiere C, Liagre B, Bianchi A, Bordji K, Dauca M, Netter P, & Beneytout JL. (2003) Different contribution of apoptosis to the antiproliferative effects of diosgenin and other plant steroids, hecogenin and tigogenin, on human 1547 osteosarcoma cells. Int J Oncol. 22, 899-905.

Corbiere C, Battu S, Liagre B, Cardot PJ, & Beneytout JL (2004a) SdFFF monitoring of cellular apoptosis induction by diosgenin and different inducers in the human 1547 osteosarcoma cell line. J Chromatogr B Analyt Technol Biomed Life Sci. 808, 255-262.

Corbiere C, Liagre B, Terro F, & Beneytout JL. (2004b) Induction of antiproliferative effect by diosgenin through activation of p53, release of apoptosis-inducing factor (AIF) and modulation of caspase-3 activity in different human cancer cells. Cell Res. 14(3): 188-196.

Chiu CS, Chiu YJ, Wu LY, Lu TC, Huang TH, Hsieh MT, Lu CY, & Peng WH. (2011) Diosgenin ameliorates cognition deficit and attenuates oxidative damage in senescent mice induced by D-galactose. Am J Chin Med. 39(3): 551-563.

Dinarello CA. (2006) The paradox of pro-inflammatory cytokines in cancer. Cancer Metastasis Rev. 25: 307-313.

Djerassi C, Rosenkranz G, Pataki J, Kaufmann S. (1952) Steroids, XXVII. Synthesis of allopregnane-3~, 11 beta, 17-, 20~, 21-pentol from cortisone and diosgenin. J Biol Chem. 194: 115-118.

Epstein J, Sanderson IR, & Macdonald TT. (2010) Curcumin as a therapeutic agent: the evidence from in vitro, animal and human studies. Br J Nutr. 103(11): 1545-1557.

Faeste CK, Namork E, & Lindvik H. (2009) Allergenicity and antigenicity of fenugreek (Trigonella foenum-graecum) proteins in foods. J Allergy Clin Immunol. 123(1): 187-194.

Fernández-Herrera MA, López-Muñoz H, Hernández-Vázquez JM, López-Dávila M, Escobar-Sánchez ML, Sánchez-Sánchez L, Pinto BM, & Sandoval-Ramírez J. (2010) Synthesis of 26-hydroxy-22-oxocholestanic frameworks from diosgenin and hecogenin and their in vitro antiproliferative and apoptotic activity on human cervical cancer CaSki cells. Bioorg Med Chem. 18(7): 2474-2484.

Flammang AM, Cifone MA, Erexson GL, & Stankowski LF Jr. (2004) Genotoxicity testing of a fenugreek extract. Food Chem Toxicol. 42(11): 1769-1775.

Juarez-Oropeza MA, Diaz-Zagoya JC, & Rabinowitz JL. (1987) In vivo and in vitro studies of hypocholesterolemic effects of diosgenin in rats. Int J Biochem. 19: 679-683.

Kosters A, Frijters RJ, Kunne C, Vink E, Schneiders MS, Schaap FG, Nibbering CP, Patel SB, & Groen AK. (2005) Diosgenin-induced biliary cholesterol secretion in mice requires Abcg8. Hepatology. 41(1): 141-150.

Kwon CS, Sohn HY, Kim SH, Kim JH, Son KH, Lee JS, Lim JK, & Kim JS. (2003) Anti-obesity effect of Dioscorea nipponica Makino with lipase-inhibitory activity in rodents. Biosci Biotechnol Biochem. 67, 1451-1456.

Lee J, Jung K, Kim YS, & Park D. (2007) Diosgenin inhibits melanogenesis through the activation of phosphatidylinositol-3-kinase pathway (PI3K) signaling. Life Sci. 81(3): 249-254.

Leger DY, Liagre B, Cardot PJ, Beneytout JL, & Battu S. (2004a) Diosgenin dose-dependent apoptosis and differentiation induction in human erythroleukemia cell line and sedimentation field-flow fractionation monitoring. Anal Biochem. 335: 267-278.

Leger DY, Liagre B, Corbiere C, Cook-Moreau J, & Beneytout JL. (2004b) Diosgenin induces cell cycle arrest and apoptosis in HEL cells with increase in intracellular calcium level, activation of cPLA2 and COX-2 overexpression. Int J Oncol. 25: 555-562.

Leger DY, Liagre B, & Beneytout JL. (2006) Role of MAPKs and NF-kappaB in diosgenin-induced megakaryocytic differentiation and subsequent apoptosis in HEL cells. Int J Oncol. 28: 201-207, 2006.

Lepage C, Liagre B, Cook-Moreau J, Pinon A, & Beneytout JL. (2010) Cyclooxygenase-2 and 5-lipoxygenase pathways in diosgenin-induced apoptosis in HT-29 and HCT-116 colon cancer cells. Int J Oncol. 36(5): 1183-1191.

Lepage C, Léger DY, Bertrand J, Martin F, Beneytout JL, & Liagre B. (2011) Diosgenin induces death receptor-5 through activation of p38 pathway and promotes TRAIL-induced apoptosis in colon cancer cells. Cancer Lett. 301(2): 193-202.

Li F, Fernandez PP, Rajendran P, Hui KM, & Sethi G. (2010) Diosgenin, a steroidal saponin, inhibits STAT3 signaling pathway leading to suppression of proliferation and chemosensitization of human hepatocellular carcinoma cells. Cancer Lett. 292(2): 197-207.

Liagre B, Vergne-Salle P, Corbiere C, Charissoux JL, & Beneytout JL. (2004) Diosgenin, a plant steroid, induces apoptosis in human rheumatoid arthritis synoviocytes with cyclooxygenase-2 overexpression. Arthritis Res Ther. 6: R373-R383.

Liagre B, Bertrand J, Leger DY, & Beneytout JL. (2005) Diosgenin, a plant steroid, induces apoptosis in COX-2 deficient K562 cells with activation of the p38 MAP kinase signalling and inhibition of NF-kappaB binding. Int J Mol Med. 16: 1095-1101.

Liagre B, Leger DY, Vergne-Salle P, & Beneytout JL. (2007) MAP kinase subtypes and Akt regulate diosgenin-induced apoptosis of rheumatoid synovial cells in association with COX-2 expression and prostanoid production. Int J Mol Med. 19: 113-122.

Liu MJ, Wang Z, Ju Y, Wong RN, & Wu QY. (2005) Diosgenin induces cell cycle arrest and apoptosis in human leukemia K562 cells with the disruption of Ca2+ homeostasis. Cancer Chemother Pharmacol. 55: 79-90.

Malisetty VS, Patlolla JMR, Raju J, Marcus LA, Choi CI, & Rao CV. (2005) Chemoprevention of colon cancer by diosgenin, a steroidal saponin constituent of fenugreek. Proc Amer Assoc Cancer Res 46 : 2473.

Marques FZ, Markus MA, & Morris BJ. (2009) Resveratrol: cellular actions of a potent natural chemical that confers a diversity of health benefits. Int J Biochem Cell Biol. 41(11): 2125-2128.

McAnuff MA, Omoruyi FO, Morrison EY, & Asemota HN. (2005) Changes in some liver enzymes in streptozotocin-induced diabetic rats fed sapogenin extract from bitter yam (Dioscorea polygonoides) or commercial diosgenin. West Indian Med J. 54(2): 97-101.

Memorial Sloan-Kettering Cancer Center. About herbs, botanicals and other products: http://www.mskcc.org/mskcc/html/11570.cfm

Moalic S, Liagre B, Corbiere C, Bianchi A, Dauca M, Bordji K, & Beneytout JL. (2001) A plant steroid, diosgenin, induces apoptosis, cell cycle arrest and COX activity in osteosarcoma cells. FEBS Lett. 506: 225-230.

Miyoshi N, Nagasawa T, Mabuchi R, Yasui Y, Wakabayashi K, Tanaka T, & Ohshima H. (2011) Chemoprevention of azoxymethane/dextran sodium sulfate-induced mouse colon carcinogenesis by freeze-dried yam sanyaku and its constituent diosgenin. Cancer Prev Res. 4(6): 924-934.

Muralidhara, Narasimhamurthy K, Viswanatha S, & Ramesh BS. (1999) Acute and subchronic toxicity assessment of debitterized fenugreek powder in the mouse and rat. Food Chem Toxicol. 37: 831-838.

Nappez C, Liagre B, & Beneytout JL. (1995) Changes in lipoxygenase activities in human erythroleukemia (HEL) cells during diosgenin-induced differentiation. Cancer Lett. 96: 133-140.

Nervi F, Marinovic I, Rigotti A, & Ulloa N. (1988) Regulation of biliary cholesterol secretion. Functional relationship between the canalicular and sinusoidal cholesterol secretory pathways in the rat. J Clin Invest. 82: 1818–1825.

Nibbering CP, Groen AK, Ottenhoff R, Brouwers JF, vanBerge-Henegouwen GP, & van Erpecum KJ. Regulation of biliary cholesterol secretion is independent of hepatocyte canalicular membrane lipid composition: a study in the diosgenin-fed rat model. J Hepatol 2001; 35: 164–169.

No authors listed. (2004) Final report of the amended safety assessment of Dioscorea Villosa (Wild Yam) root extract. Int J Toxicol. 23: 49-54.

Omoruyi FO. (2008) Jamaican bitter yam sapogenin: potential mechanisms of action in diabetes. Plant Foods Hum Nutr. 63(3): 135-140.

Qin Y, Wu X, Huang W, Gong G, Li D, He Y, & Zhao Y. (2009) Acute toxicity and sub-chronic toxicity of steroidal saponins from Dioscorea zingiberensis C.H.Wright in rodents. J Ethnopharmacol. 126(3): 543-650.

Raju J, & Bird RP. (2007) Diosgenin, a naturally occurring steroid [corrected] saponin suppresses 3-hydroxy-3-methylglutaryl CoA reductase expression and induces apoptosis in HCT-116 human colon carcinoma cells. Cancer Lett. 255(2): 194-204.

Raju J, & Bird RP. (2006) Alleviation of hepatic steatosis accompanied by modulation of plasma and liver TNF-alpha levels by Trigonella foenum graecum (fenugreek) seeds in Zucker obese (fa/fa) rats. Int J Obes. 30(8): 1298-1307.

Raju J, & Mehta R. (2009) Cancer chemopreventive and therapeutic effects of diosgenin, a food saponin. Nutr Cancer. 61(1): 27-35.

Raju J & Rao CV. (2009) Molecular Targets and Therapeutic uses of Fenugreek (Diosgenin). In: Molecular Targets and Therapeutic uses of Spices: Modern Uses for Ancient Medicine Aggarwal BB and Kunnumakkara AB (Eds.) pp 173-196, World Scientific Publishing Company Inc., Hackensack, New Jersey.

Raju J, Patlolla JM, Swamy MV, & Rao CV. (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 Epidemiol Biomarkers Prev. 13: 1392-1398.

Saito ST, Gosmann G, Pungartnik C, & Brendel M. (2009) Green tea extract-patents and diversity of uses. Recent Pat Food Nutr Agric. 1(3): 203-215.

Sauvaire Y, Petit P, Baissac Y, & Ribes G. (2000) Chemistry and pharmacology of fenugreek. In: Herbs, botanicals and teas. Mazza G and Oomah BD (Eds.) pp 107–129, Technomic Pub. Co., Lancaster, Pensylvannia.

Shishodia S, & Aggarwal BB. (2006) Diosgenin inhibits osteoclastogenesis, invasion, and proliferation through the down-regulation of Akt, I kappa B kinase activation and NF-kappa B-regulated gene expression. Oncogene. 25: 1463-1473.

Srinivasan S, Koduru S, Kumar R, Venguswamy G, Kyprianou N, & Damodaran C. (2009) Diosgenin targets Akt-mediated prosurvival signaling in human breast cancer cells. Int J Cancer. 125(4): 961-967.

Son IS, Kim JH, Sohn HY, Son KH, Kim JS, & Kwon CS. (2007) Antioxidative and hypolipidemic effects of diosgenin, a steroidal saponin of yam (Dioscorea spp.), on high-cholesterol fed rats. Biosci Biotechnol Biochem. 71: 3063-3071.

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

Taylor WG, Elder JL, Chang PR, & Richards KW. (2000) Microdetermination of diosgenin from fenugreek (Trigonella foenum-graecum) seeds. J Agric Food Chem. 48: 5206-5210.

Temel RE, Brown JM, Ma Y, Tang W, Rudel LL, Ioannou YA, Davies JP, & Yu L. (2009) Diosgenin stimulation of fecal cholesterol excretion in mice is not NPC1L1 dependent. J Lipid Res. 50(5): 915-23.

Thirunavukkarasu V, Anuradha CV, & Viswanathan P. (2003) Protective effect of fenugreek (Trigonella foenum graecum) seeds in experimental ethanol toxicity. Phytother Res. 17(7): 737-43.

Trouillas P, Corbiere C, Liagre B, Duroux JL, & Beneytout JL. (2005) Structure-function relationship for saponin effects on cell cycle arrest and apoptosis in the human 1547 osteosarcoma cells: a molecular modelling approach of natural molecules structurally close to diosgenin. Bioorg Med Chem. 13, 1141-1149.

Turchan-Cholewo J, Liu Y, Gartner S, Reid R, Jie C, Peng X, Chen KC, Chauhan A, Haughey N, Cutler R, Mattson MP, Pardo C, Conant K, Sacktor N, McArthur JC, Hauser KF, Gairola C, & Nath A. (2006) Increased vulnerability of ApoE4 neurons to HIV proteins and opiates: protection by diosgenin and L-deprenyl. Neurobiol Dis. 23: 109-119.

Uemura T, Hirai S, Mizoguchi N, Goto T, Lee JY, Taketani K, Nakano Y, Shono J, Hoshino S, Tsuge N, Narukami T, Takahashi N, & Kawada T. (2010) Diosgenin present in fenugreek improves glucose metabolism by promoting adipocyte differentiation and inhibiting inflammation in adipose tissues. Mol Nutr Food Res. 54(11): 1596-1608.

U lbricht C, Basch E, Burke D, Cheung L, Ernst E, Giese N, Foppa I, Hammerness P, Hashmi S, Kuo G, Miranda M, Mukherjee S, Smith M, Sollars D, Tanguay-Colucci S, Vijayan N, & Weissner W. (2007) Fenugreek (Trigonella foenum-graecum L. Leguminosae): an evidence-based systematic review by the natural standard research collaboration. J Herb Pharmacother. 7: 143-177.

Wang YJ, Pan KL, Hsieh TC, Chang TY, Lin WH, & Hsu JT. (2011) Diosgenin, a plant-derived sapogenin, exhibits antiviral activity in vitro against hepatitis C virus. J Nat Prod. 74(4): 580-584.

Wojcikowski K, Wohlmuth H, Johnson DW, & Gobe G. (2008) Dioscorea villosa (wild yam) induces chronic kidney injury via pro-fibrotic pathways. Food Chem Toxicol. 46(9): 3122-3131.

Yamada T, Hoshino M, Hayakawa T, Ohhara H, Yamada H, Nakazawa T, Inagaki T, Iida M, Ogasawara T, Uchida A, Hasegawa C, Murasaki G, Miyaji M, Hirata A, & Takeuchi T. (2009) Dietary diosgenin attenuates subacute intestinal inflammation associated with indomethacin in rats. Am J Physiol. 273: G355-G364.

Yan LL, Zhang YJ, Gao WY, Man SL, & Wang Y. (2009) In vitro and in vivo anticancer activity of steroid saponins of Paris polyphylla var. yunnanensis. Exp Oncol. 31(1): 27-32.

Yu ZY, Guo L, Wang B, Kang LP, Zhao ZH, Shan YJ, Xiao H, Chen JP, Ma BP, & Cong YW. (2010) Structural requirement of spirostanol glycosides for rat uterine contractility and mode of their synergism. J Pharm Pharmacol. 62: 521-529.

Bioactive Compounds in Phytomedicine

Edited by Prof. Iraj Rasooli

There are significant concerns regarding the potential side effects from the chronic use of conventional drugs such as corticosteroids, especially in children. Herbal therapy is less expensive, more readily available, and increasingly becoming common practice all over the world. Such practices have both their benefits and risks. However, herbal self-therapy might have serious health consequences due to incorrect self-diagnosis, inappropriate choice of herbal remedy or adulterated herbal product. In addition, absence of clinical trials and other traditional safety mechanisms before medicines are introduced to the wider market results in questionable safe dosage ranges which may produce adverse and unexpected outcomes. Therefore, the use of herbal remedies requires sufficient knowledge about the efficacy, safety and proper use of such products. Hence, it is necessary to have baseline data regarding the use of herbal remedies and to educate future health professionals about various aspects of herbal remedies.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

INTECH
open science | open minds