2. REVIEW OF LITERATURE

Chapter 2 deals extensively on the review about *Dioscorea bulbifera* Linn and one of its bioactive molecule diosgenin in literature.

*Dioscorea* is a large genus of annual twining herbs, distributed throughout the moist tropics of the world and extending into warm temperate regions. About 50 species are found in India; a large number among them occur in the wild state and a few are cultivated for their edible tubers. The yams of several species are soft, fleshy and edible. Those wild species are sought for by animals, and most species have protective adaptations against such predators. Yams form a cheap source of carbohydrate food and are extensively used by hill tribes in the uncultivated tracts of Assam, Bihar, Bengal, Madhya Pradesh, Orissa and Deccan. They are of inestimable value during periods of scarcity. The alkaloid, dioscorine and the saponin dioscin occur in varying quantities in different species of yams. Some of the American species of the genus are reported to contain steroidal sapogenins, diosgenin, yamogenin, kryptogenin and others. Among the species of this genus *bulbifera* is widely used as medicine and also as a food.

2.1 ETHNOBOTANY OF *Dioscorea bulbifera* LINN.

*Dioscorea bulbifera* Linn. (Family: Dioscoreaceae) is described in Ayurvedic system of medicine as Varahikanda, Charmakarakula, Varahavadana, Grishti and Varada. The plant is distributed commonly throughout India ascending upto 1800 m in the Himalayas and parts of Chotanagpur, Bihar, Orissa, West Coast and along the whole of the East coast districts. It is also widely cultivated in the Konkan region. It is also found in Nepal, China and United States. The Ayurvedic preparation such as Narasimha-churna
and Shivagutika contains this material as one of the ingredients. The parts used for medicinal use is the tuber.

2.2 **SYNONYMS**

*Dioscorea crispata* (Roxb.)

*Dioscorea pulchella* (Roxb.)

*Dioscorea sativa* (Thunb. non Linn.)

*Dioscorea versicolor* (Buch.-Ham. ex Wall)

2.3 **VERNACULAR NAMES**

- **English**: Yam.
- **Hindi**: Ratalu, Suaralu, Pitaalu, Zamin Kand.
- **Bengali**: Banalu, Kukuralu, Gaicha, Slu.
- **Gujarati**: Goradu.
- **Kanada**: Heggenasu.
- **Malayalam**: Kattu, Kachil.
- **Marathi**: Manakund, Konfa goradu, Karanda, Karukarinda, Gathalu.
- **Tamil**: Kodikilangu, Pannukilangu.
- **Telugu**: Chedupaddu dumpa, Malkakayapendalamu.

2.4 **MORPHOLOGICAL FEATURES**

*Dioscorea bulbifera* Linn. is a perennial herb. It has a large unarmed climber with stems twining towards the left. Leaves are alternate, simple and broadly ovate-cordate. Male spikes 6.5 – 10.0 cm long, female spikes 10-25 cm long. Capsules quadrately oblong, 1.7-2.5 x 0.5 cm, reflexed, three winged. Seeds winged at one end. Tubers are solitary, very variable globose to pyriform usually small and round, skin purplish black or
earth-coloured, usually coated with abundant small feeding roots but smoothened in some cultivated varieties. Prominent eyes are also seen over the tuber. Flesh of the tuber appears white to yellow, sometimes marked with purple flecks and very mucilaginous. Bulbils are common, axillary, roundish and brown with numerous, uniformly distributed tubercle like eyes. The aerial and tubers are shown in Figure 2.1.

**Figure 2.1**  *Dioscorea bulbifera* Linn. Tuber and Aerial Part
2.5 MEDICINAL PROPERTIES

The tuber is bitter, acrid, thermogenic and mostly used as a famine food. It is purgative, deflatulent, aphrodisiac, rejuvenating, tonic, anti-helmentic and is used in haematological disorders, scrofula, syphilis, haemorrhoids, flatulence, diarrhea, dysentery, worm infestations, general debility, diabetic disorders, polyuria and skin disorders. The tubers are crushed and made decoction that is emulsified into oil, which is used in infected ulcers, sinus and pus pockets. Tubers are also used in the preparation of starch (Sharma et al., 2000).

2.6 PHYTOCONSTITUENTS OF Dioscorea bulbifera Linn.

Martin et al., (1974) reported the presence of some yellow coloured pigments from the aerial tubers of D. bulbifera Linn. The major part of the yellow colour is saponifiable esters of xanthophylls. Small quantities of xanthophylls in the free state are identified as lutein, neoxanthin, violaxanthin, auroxanthin and cryptoxanthin. Other pigments present include chlorophylls, anthocyanins and unidentified phenolics.

Bitter and related non bitter compounds were extracted from the tubers of D. bulbifera Linn. by Telek et al., (1974), they are terpenoids with the resemblance to furanoid norditerpenes.

8-epidosbulbin E acetate and 18-norclerodane diterpenoid have been isolated from the tubers of D. bulbifera Linn. for the first time by Murray et al., in 1984. Besides these compounds they have also isolated previously known norditerpenoid, diosbulbin D.

Gupta and Singh (1989) have isolated two new p-hydroxy acetophenone derivatives namely 4-hydroxy-[2-trans-3’, 7’-dimethyl-octa-2’, 6’-dienyl]-6-methoxy
acetophenone and 4,6-dihydroxy-2-O-(4′-hydroxybutyl)acetophenone from the bulbs of *D. bulbifera* Linn.

Adesanya *et al.*, (1989) have analysed the ethyl acetate extract of the bulbil of *D. bulbifera* Linn. and the tuber of *Dioscorea dumentorum* infected with *Botryodiplodia theobromae* and isolated Demethylbatatasin IV and a new dihydrostilbene, 3,5,4′-tri hydroxybibenzyl (dihydroresveratrol) respectively, as their major phytoalexins.

Yonemitsu *et al.*, (1993) have presented the presence of Diosbulbin-B from the leaves and stems of *D. bulbifera* Linn. with spectral data. Komori T (1997) has isolated eight substances namely Diosbulbin A-H as well as two structurally analogous non-conjugated enolglycosides, Diosbulbinosides D and F from the tubers of *D. bulbifera* Linn. Moreover, the studies with Diosbulbin A, B and Diosbulbin A-2-O-β-D-glucopyranoside have shown that all the three compounds possess a remarkable growth inhibition effect.

Li *et al.*, (2000) have isolated three compounds for the first time from *D. bulbifera* Linn. and elucidated as 3,7-dimethoxy-5,4′-dihydroxyflavone; 3,7-dimethoxy-5,3′,4′-trihydroxyflavone and emodin. Gao *et al.*, (2001) have isolated another seven compounds from *D. bulbifera* Linn.

Zheng *et al.*, (2003) have added another three new apianen lactone compounds along with four known compounds the structure of the compound was elucidated on the basis of spectral and chemical means.

Tang *et al.*, (2006) have developed a novel method for separation and determination of epicatechin, isovanillic acid and myrcetin from *D. bulbifera* Linn. and identify its medicinal preparations.
Teponno et al., (2006b) have introduced Bafoudiosbulbins A1 and B2 together with five known compounds such as tetracosanoic acid, 1-(tetracosanoyl)-glycerol, trans-tetracosanylferrulate, \( \beta \)-sitosterol and 3-O-\( \beta \)-D-glucopyranosyl-\( \beta \)-sitosterol from the tubers of *D. bulbifera* Linn. Moreover, when the dichloromethane soluble portion of the crude extract and the two clerodane diterpenoids, Bafoudiosbulbin A1 and B2 subjected to anti-microbial studies, exhibited significant anti-bacterial activity against *Pseudomonas aeruginosa*, *Salmonella typhi*, *S.paratyphi A* and *S.parathphi B*.

Teponno et al., (2006a) have extracted pennagenin Spiroconazole A, a steroidal saponin from the tuber. Also they have isolated four polyphenolic substances such as dihydroxy-4- methoxy phenanthrene, Quercetin, Quercetin-3-O-\( \beta \)-D-glucopyranoside and Quercetin-3-O-\( \beta \)-D-galactopyranoside.

### 2.7 Nutritional and Anti-nutritional Aspects of *Dioscorea bulbifera* Linn.

Ragunadhan and Jolly (1987) have for the first time parted away and studied the characteristics of the starch from *D. bulbifera* Linn. Rincon et al., (2000) have compared the chemical composition and physical characters of two Dioscorea tubers and found that *D. bulbifera* Linn. tubers have low protein content when compared to *D. trifida* and *D. bulbifera* Linn. can be used in the development of instant soup mixes. Bhandari et al., (2003) have related the nutritional components of wild yams of Nepal and they found that nutritional composition of wild yams were similar when compared with the several parts of the world with exception, dietary fiber with higher value. Later, they have also reported the presence of anti-nutritional factors such as oxalates, cyanogens, trypsin inhibitor activity and alpha-amylase inhibitory activity of three Dioscorea species.
including *D. bulbifera* Linn. and suggested that proper processing of food has to be carried out to eliminate the effect of antinutrients (Bhandari and Kawabata, 2004).

Araujo de Vizcarrondo *et al.*, (2004) have evaluated the starch from bulbils of *D. bulbifera* Linn. and conveyed that these starches can be used in food products that need fast viscosity and gel with a stable consistency.

Sahore and Amani (2005) have studied the proximate analysis and mineral contents of seven species of wild yam. Again Bhandari and Kawabata (2006) have assessed the effect of cooking on the anti-nutritional factors seen in raw wild yam and showed that cooking of yam results in reduction in antinutrients. Sahore *et al.*, (2007) have removed starch from bulbils and tubers of wild yams and evaluated their paste viscosity and clarity, iodine binding and syneresis.

### 2.8 Pharmacological and Toxicological Studies

Jindal *et al.*, (1969) have carried out a preliminary work to study the anorexiant property of *D. bulbifera* Linn. Later Song (1983) had registered the toxicity of *D. bulbifera* Linn. On rat liver and kidney.

Webster *et al.*, in 1984 have demonstrated that when underground tubers of *D. bulbifera* Linn. are subjected to acute toxicity in rats they are non toxic. He also proposed that bitterness of the tuber was due to the presence of Diosbulbin D and the traditional food processing techniques are found to be effective in removing Diosbulbin D, thus making it palatable.

Adeleye and IKotun (1989) have reported that dihydrodioscorine extracted from the wild variety of *D. bulbifera* Linn. is found to have anti-fungal activity. Later in 1995
Niikawa has displayed that 60 % ethanolic extract of *D. bulbifera* Linn. has significant inhibitory activity against mutagenicity induced by TRP-P-1.

Gao et al., (2002) have for the first time reported about the presence of anti-tumor promoting activity of this plant. The ethyl acetate soluble fraction of the 75 % alcoholic extract of rhizome and their phyto-constituents namely Kaempferol-3,5-dimethyl ether, Caryatin, (+)-Catechin, Myricetin, Quercetin-3-O-galactopyranoside, Myricetin-3-O-galactopyranoside, Myricetin-3-O-glucopyranoside and Diosbulbin B have shown anti-tumor promoting activity against the tumor promotion in JB6 cells induced by 12-O-Tetradecanoylphorbol-13-acetate (TPA).

Tan et al., (2003) have examined direct bilirubin and glutamate pyruvate transaminase and measured the liver index in rats treated with 10 % total methanol, 5 % chloroform fraction and 5 % methanol fraction, respectively and he has found that the chloroform fraction is the liver toxic fraction when compared with the control group. Later Su et al., (2003) have studied the pathological changes and the toxic mechanisms in mice which was subjected to sub-acute intoxication with different doses of *D. bulbifera* Linn. The experiment has suggested that the target organs of the intoxications are liver and kidney by damaging the mitochondrial and endoplasmic reticulum membrane which results in the decrease in succinate dehydrogenase and glucose-6-phosphate, thereby affecting the metabolism.

Yu et al., (2004) have investigated the anticancer effects of various fractions extracted from *D. bulbifera* Linn. and found that active anticancer compounds are mainly extracted by petroleum ether. Later Chen (2006) have looked into the mechanism of liver injury caused *D. bulbifera* Linn. at the level of gene expression and they have found that
when mice are treated with *D. bulbifera* Linn. for 15 days, 83 genes where expressed differentially and serum ALT, AST and tissue total protein are increased. However, when the mice are treated for 30 days 1658 genes are differentially expressed and the serum ALT and tissue total protein are increased with significant decrease in AST and ALP indicating the change in liver mouse cell expression profile.

Zhang *et al.*, (2007) have extracted polysaccharides from the tubers using ultrasound which have anti-tumor activity. Shriram *et al.*, (2008) have carried out bioassay guided fractionation of aqueous methanolic extract of *Dioscorea bulbifera* Linn. and identified that 8-epidosbulbin E acetate (EEA) a norditerpene has broadspectrum plasmid curing activity against multidrug resistance bacteria. Moreover, it is also reported that EEA does not show any cytotoxicity against broad range of human cancer cell.

### 2.9 DIOSGENIN AND *Dioscorea bulbifera* Linn.

Diosgenin a steroidal saponin belonging to the sapogenin group, is the principle active constituent of *Dioscorea bulbifera* Linn. However, the percentage of composition varies with area of distribution. In 1965 Akira Akahori has analysed the steroidal sapogenins in twelve Japanese species of *Dioscorea sps.* including *Dioscorea bulbifera* Linn. and reported that *Dioscorea sps.* which have opposite leaves, stems twining to the right and edible roots do not contain sapogenins. *Dioscorea bulbifera* Linn. which has stems twining to the left and globose tuber and forms bulbils, also do not contain sapogenins. However Indian varities of *Dioscorea bulbifera* Linn contains diosgenin (Sharma *et al.*, 2000).
2.9.1 EFFECT OF DIOSGENIN ON LIPID METABOLISM

Diosgenin a steroidal saponin, when treated for one week in combination with Clofibrate reverses hyperlipoproteinemia significantly, when compared with the individual treatment of clofibrate and diosgenin by reducing the LDL cholesterol. Clofibrate does not alter the effectiveness of diosgenin in reducing cholesterol absorption (Cayen and Dvornik, 1978). Later, Cayen and Dvornik (1979) have studied the effect of diosgenin on lipid metabolism using serum isotope ratio technique and they have concluded that diosgenin is more active than cholestyramine and β-sitosterol in suppressing the serum and liver uptake of cholesterol. Diosgenin reduces the serum LDL and increases the HDL level in cholesterol fed rats and they do not alter the cholesterol level in normal rats. Diosgenin also interferes with the absorption of cholesterol of both exogenous and endogenous origin; such interference is accompanied by derepressed, i.e., increased, rates of hepatic and intestinal cholesterol synthesis. The increased unabsorbed cholesterol together with enhanced secretion of cholesterol into bile resulted in increased excretion of neutral sterols without affecting the biliary and fecal excretion of bile acids.

Diosgenin is poorly absorbed in rats, dogs and squirrel monkeys when given a single oral dose and the absorbed amount undergoes extensive transformation. Moreover, the patterns of metabolites were also dissimilar within species (Cayen et al., 1979).

In 1982, Odumosu has reported that cholesterol lowering action of clofibrate and diosgenin is enhanced with daily supplement of vitamin C in hypercholesterolemic guinea-pigs. Uchida et al., (1984) have examined the changes in bile acid metabolism in CRJ: CD-1 male mice fed with 1 % diet of diosgenin and there is no significant change in the body weight with response to diosgenin. However, decrease in cholesterol absorption,
liver cholesterol level, increased faecal excretion of cholesterol and decreased faecal excretions of bile acids are observed.

Ulloa and Nervi (1985) have reported that the plant steroid induced biliary cholesterol output which is independent of the inputs of cholesterol from diet and from hepatic cholesterogenesis is modified by the plant steroid. And the changes in biliary cholesterol secretion are the consequence of direct effects of the steroids on the intra-hepatocytic regulatory mechanisms of biliary cholesterol secretion.

Malinow et al., (1987) have synthesized diosgenin glucoside with predominant β anomer and tested its effect on cholesterol homeostasis in monkeys and reported that these glycosides may be used in the management of hypercholesterolemia and atherosclerosis.

In-vivo and in-vitro studies of hypercholesterolemic effects of diosgenin in rats demonstrated by Juarez-Oropeza et al., (1987) have shown that diosgenin decreased plasma cholesterol levels in rats, 12 % of the ingested diosgenin is distributed throughout liver, spleen, epididymal fat, brain and carcass of rat. Diosgenin is better absorbed in gut than cholesterol and diosgenin is found as esters in tissues and cholesterol is less esterified in the presence of diosgenin.

When supplemented 1 % diosgenin to rats for a week, it has caused the appearance of vesicular lipid in fistula bile (Holland et al., 1993). Thewles et al., (1993) have reported that diosgenin induced elevation of biliary cholesterol output is bile salt dependant and exhibits a shift in biliary cholesterol transport to higher molecular-mass structures.
Roman *et al.*, (1995) have studied the reasons for elevated biliary cholesterol in rats, fed with diosgenin for a week and found that there might be possibly involvement of cytosolic lipid binding proteins as lipid carriers to the canalicular membrane as an alternative to the presence of the lipid in lipid supply vesicles.

Accatino *et al.*, (1998) have reported that diosgenin feeding attenuated the acute cholestatic effect of estradiol-17-β-D-glucuronide and diosgenin induced increase of bile cholesterol and lipid lamellae are not apparent when diosgenin fed rats received 17α-ethynylestradiol. Despite this, diosgenin administration has prevented some cholestatic effect of 17α-ethynylestradiol through different metabolic effects and direct membrane effects, not related to increased lipid lamellae excretion.

Amigo *et al.*, (1999) have undertaken a study to characterise the role of plasma membrane cholesterol in canicular secretory functions and hepatocyte integrity against intravenous taurocholate administration and found that the diosgenin fed rats shown delayed release of the enzymes glutamic oxalacetic transaminase, lactic dehydrogenase, and alkaline phosphatase activities in bile. Moreover, it is associated with the increased concentration of cholesterol and sphingomyelin in canalicular membrane.

Ma *et al.*, (2002) have compared the anti-hypercholesterolemic and cholesterol absorption inhibitory activity between total saponin of *Dioscorea panthaica* (TSDP) and diosgenin and found that diosgenin has given significant anti-hypercholesterolemic effect at doses of 80 mg/kg and 160 mg/kg in mice, when compared with TSDP. However, diosgenin when treated at 20 and 40 mg/kg intraperitoneally have also revealed significant effect and when pre-treated with 100 and 200 mg/kg through intragastric route it has indicated significant effect. Diosgenin has also marked strong inhibitory effect on
cholesterol micelle formation; these effects of diosgenin might be due to its cholesterol inhibitory activity.

Kwon et al., (2003) have proved that diosgenin from Dioscorea nipponica can suppress blood triglyceride level when it is orally injected with corn oil to mice, suggesting the potentiality of diosgenin to inhibit fat absorption.

Diosgenin has also enhanced the cholestatic effect of estradiol by enhancing the hepatic abcg5 and abcg8 gene expression (Kamisako and ogawa 2005). Diosgenin induces biliary cholesterol secretion in mice which requires Abcg8 expression and upregulated Srebp2 expression in mice (Kosters et al., 2005).

2.9.2 ROLE OF DIOSGENIN IN DIABETIC CONDITION

In 2001 Al-Habori et al., have established that diosgenin has a capacity to inhibit intestinal absorption of glucose in-vitro with IC$_{50}$ value of 8 mM and it has also inhibited glucagon-induced hepatic glycogen phosphorylase-a (HGPa) activity by 20% at 4 mM concentration. Later McAnuff et al., (2002) have directed that diosgenin can also reduce the blood glucose level in-vivo in streptozotocin induced diabetic rats and it can be used in the management of hypercholesterolemia due to diabetes. Recently, it has been confirmed by in-vitro and in-vivo studies that diosgenin exerts hypoglycemic, hypocholesterolemic and hypertriglyceridemia modulated by PPAR’s in NIDDM (Sangeetha et al., 2013). Moreover it has been identified that Diosgenin alleviated diabetes induced oxidative stress as evidenced by the activity of the antioxidant enzymes.

Diosgenin has also a capability to decrease the villus length in streptozotocin induced diabetic rats thereby bringing alterations in the intestinal morphology and absorption (McAnuff et al., 2003) and it has also brought about the changes in liver
enzymes and thereby reduces the plasma glucose concentration (McAnuff et al., 2005a). Diosgenin has also increased the $\alpha$-amylase activity in the proximal region of the small intestinal mucosa and reduced $\text{Na}^+\text{-K}^+$-ATPase activity, increased $\text{Ca}^{2+}$ ATPase in the proximal region. However, the hypoglycaemic activity might be due to $\text{Na}^+\text{-K}^+$-ATPase in the intestine exerted by diosgenin in diabetic rats (McAnuff et al., 2005b) and it has also reduced the disaccharidases activity (McAnuff et al., 2006).

Omoruyi et al., (2006) have studied the effect of diosgenin on faecal minerals and intestinal lipids in streptozotocin induced diabetic rats and found that diosgenin significantly alter the faecal magnesium, zinc and calcium but there is a decrease in sodium and potassium excretion in the faeces. There is also increase in lipid excretion in diabetic rats treated with diosgenin and decrease in lipid content in the intestine.

2.9.3 HORMONE LIKE ACTIVITY OF DIOSGENIN

Aradhana et al., (1992) have reported the presence of estrogenic action of diosgenin on the mammary epithelium of ovariectomized mouse when administered with subcutaneous administration of diosgenin (20 and 40 mg/kg body weight) for 15 days. However, its action is augmented when diosgenin is administered concomitantly with estrogen.

Diosgenin when it is given to ovariectomised rat using tricalcium phosphate lysine drug delivery systems (TCPL) significantly reduces the serum malondialdehyde on treatment for 47 days (Scott et al., 2000). Later, in 2001 Scott et al., have studied the effect of TCPL drug delivery system using diosgenin, dehydroepiandrosterone and estradiol in the prevention of osteoporotic progression due to hormonal imbalance. However, Higdon et al., (2001) while using the above said three steroids in sustained
delivery settings have concluded that these three steroids can be handy when it is used as a supplement to reduce bone loss after ovariectomy.

Tricalcium phosphate (TCP) drug delivery system loaded with 500 mg of diosgenin decreases the cortical and medullary adrenal areas when treated to ovariectomized rats suggesting the potential of diosgenin in endocrine complication (Benghuzzi et al., 2003). Later Tucci and Benghuzzi (2003) have reported that TCP impregnated to diosgenin protects the morphological changes of kidney associated with ovariectomy. The mechanism underlying for this activity might be conversion of diosgenin to progesterone. Hsu et al., (2008) have found that diosgenin does not modify the expression of calpain isoforms in ovariectomised rats.

2.9.4 ANTI-INFLAMMATORY ACTIVITY OF DIOSGENIN

Yamada et al., (1997) have investigated the effect of dietary diosgenin on indomethacin induced intestinal inflammation and alterations in bile secretion in rats and reported that diosgenin dose dependently attenuated subacute intestinal inflammation and normalised bile secretion, it may also compromise the anti-inflammatory action of Indomethacin.

2.9.5 ANTI-CANCER ACTIVITY OF DIOSGENIN

Beneytout et al., (1995) have investigated the effect of certain plant steroids including diosgenin on the human erythroleukemia cell line (HEL TIB 180) and found that diosgenin induces morphological and biochemical changes characteristic of megakaryocyte cells. Diosgenin also has the capacity to inhibit human osteosarcoma 1547 cell line in G1 phase and apoptosis induction by eliciting the expression of p53, p21
mRNA, activation of NF-kappaB and it has also shown a time dependent increase in PGE$_2$ synthesis (Moalic et al., 2001).

In 2003 Corbiere et al., have found that diosgenin induces NF-kappaB and thereby binds to DNA and increases the p53 protein expression which contributes to its anti-proliferative effect. Diosgenin has also indicated anti-tumor activity on S-180, HepA, U14 transplant mice in-vivo and L929, HeLa, MCF cells in-vitro (Wang et al., 2002). Later, Hou et al., (2004) have investigated the mechanism of diosgenin induced Hela cell apoptosis and found that diosgenin brought about by the reduction of mitochondrial membrane potential and down regulated the Bcl-2 expression and concluded that diosgenin induces HeLa cell apoptosis through caspase pathway.

Diosgenin and its derivatives are found to have cytotoxic activity in V79 fibroblasts than in hepatocytes and they are not detoxified through cytochrome P450 IIIA (Melo et al., 2004).

Liu et al., (2005) have reported that diosgenin inhibits K562 cell proliferation via cell cycle G2/M arrest and apoptosis, with disruption of Ca$_{2+}$ homeostasis and mitochondrial dysfunction playing vital roles. Likewise, Li et al., (2005) have pointed out that diosgenin can effectively inhibit the viability and proliferation of the breast cancer cells MCF-7.

Shishodia and Aggarwal (2006) have brought out that diosgenin suppresses proliferation, inhibits invasion, and suppresses osteoclastogenesis through inhibition of NF-kappaB-regulated gene expression and enhances apoptosis induced by cytokines and chemotherapeutic agents.
Raju and Bird (2007) have studied the anticancer effect of Diosgenin in HCT-116 Human colon carcinoma cells and proved that diosgenin can inhibit the growth and induce apoptosis and it also supresses the expression of HMG CoA reductase in a dose dependent manner. Cailleteau et al., (2008) have reported that diosgenin induces the COX-2 and thromboxane synthase expression in human erythroleukemia cells and thereby, induces megakaryocytic differentiation.

2.9.6 Anti-Arthritic Activity

Liagre et al., (2004) have for the first time reported that diosgenin can cause an inhibition of the growth of fibroblast like synoviocytes from human rheumatoid arthritis, with apoptosis induction associated with cyclooxygenase-2 up regulation. Diosgenin also has antiproliferative effect in different cell lines of human such as laryngocarcinoma Hep-2 and melanoma M4Beu cells by inducing apoptosis through caspase-3 dependent pathway with a fall of mitochondrial membrane potential, nuclear localisation of Apoptosis induction factor and poly (ADP-ribose) polymerase cleavage. Diosgenin also induces p53 activation and cell cycle arrest in the different cell lines. Later, Liagre et al., (2005) have for the first time suggested that inhibition of NF-kappaB nuclear binding and p38 MAPK activation are involved in diosgenin-mediated signal cascades in K562 cells for inducing/regulating DNA fragmentation.

Recently, Liagre et al., (2007) have investigated the signalling pathways involved in diosgenin-induced apoptosis in human rheumatoid arthritis fibroblast like synoviocytes (RA-FLS) and indicated that implicating the combined association of MEK inhibitor and diosgenin is effective in inducing strong apoptosis with down-regulation of COX-2 expression and activity in human RA-FLS.
2.9.7 **CHOLERECTIC ACTIVITY**

Yamaguchi *et al.*, (2003) have studied about the choleretic action of diosgenin and concluded that cholerectic activity of diosgenin is based upon both the direct stimulation of transporter expression and indirect transporter activation by an increase of membrane fluidity.

2.9.8 **VASODILATING ACTIVITY**

Au *et al.*, (2004) have studied the vasodilating effect of diosgenin using porcine resistance left anterior descending coronary artery and found that disogenin vasodilating effect is acute and its endothelium-independent coronary artery relaxation is through protein kinase G signalling cascade and activation of Ca$^{2+}$ channel of arterial smooth muscle cells. It is found that oestrogen receptor (alpha and beta-isoforms) and progesterone receptor are probably not involved.

2.9.9 **UP-REGULATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR**

Yen *et al.*, (2005) have extracted diosgenin from the root of *Dioscorea villosa* and proved that diosgenin up-regulates vascular endothelial growth factor-A and promotes angiogenesis in pre-osteoblast like cells by a hypoxia-inducible factor-1alpha-dependent mechanism involving the activation of src kinase, p38 MAPK, and Akt signaling pathways via estrogen receptor.

2.9.10 **HEPATOPROTECTIVE EFFECT**

Kondeva *et al.*, (2006) have reported the effect of diosgenin on freshly isolated hepatocytes treated with tert-butyl hydroperoxide.
2.9.11 STIMULATION OF ION CURRENT IN NEURONAL CELLS

Wang et al., (2006) have reported that diosgenin can actively stimulate the Ca\textsuperscript{2+}-activated K\textsuperscript{+} current in human cortical HCN-1A neuronal cells and thereby, it can affect the functional activity of cortical neurons.

2.9.12 IMMUNOMODULATORY ACTIVITY

Diosgenin modulates certain aspects of acquired immunity, including the enhancement of antigen specific IgG2a and IFN-gamma expression by upregualting Th1 differentiation (Jan et al., 2007). It also inhibits the melanogenesis through the activation of phosphatidylinositol-3-kinase pathway.

Based on its potential in various biological activities it was found worth studying the cardioprotective potential of Diosgenin and Dioscorea bulbifera Linn. and its probable mode of action in a scientific manner and also substantiate its use in traditional medicine and translate the same for use as a nutraceutical/pharmaceutical lead in future.