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Ethnopharmacological Potential and Medicinal Uses of Miracle Herb *Dioscorea* spp.

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ABSTRACT

Dioscorea a well-known source of Diosgenin-steroid raw material, is one of the oldest tuber crop cultivated or harvested from wild in the tropical region throughout the world and make up one of the chief food items for a number of tribal groups. In India there are about 50 species of *dioscorea*, mainly found in North-East region which is rich in tropical root and tuber crops. *Dioscorea* produces rhizomes or bulbils, which are having rich medicinal and economic value. The rhizomes are used for the treatment of different diseases like cardiovascular system disorders, central nervous system disorders, disease of bones and joint metabolic disorder, disgestive disorders, sore throat for struma, diarrhea, irritability, abdominal pain, dysfunctional changes in the female reproductive system, skin diseases, oncology and immune deficiency and autoimmune diseases, anti-diabetes, neuroprotectiveused, decrease oxidative stress and many more disordered conditions. Diosgenin is a precursor for the chemical synthesis of drug like steroids and has a great importance for pharmaceutical industry. *Dioscorea* contains various bioactive chemical substances like diosgenin, corticosterone, and sigmasterol, which are of great market value. The current study is to appraise the medicinal properties, phytochemicals, and pharmacological activities of *Dioscorea*.

Keywords: *Dioscorea*, chemical constituents, pharmacological activities.

INTRODUCTION

Dioscorea species is a climber herb with rhizomatous rootstook. It belongs to the family Dioscoreaceae. The genus *Dioscorea* belongs to division Monocotyledon comprises 350-400 species. Dioscorea is spread all over the tropics and subtropical regions in the world, 96% production occur in Africa. Other production centers are South America, the Caribbean islands and also found in South East Asia [1]. *Dioscorea* is a perennial plant, growing up to 3m (10 ft) in height. Rhizomes are ligneous asymmetrical, alternately arranged. Leaves are simple, 5-11.5cm long, 4-10.5cm broad, triangular ovate, often heart-shaped, 7- 9 nerved, long pointed, both sides smooth and glabrous, petiole slender, 5-10cm long. Male flowers in leaves axils, simple or sometimes branched, slender, flexible, 7.5-25cm long. Flowers tiny, secluded in clusters; stamens 6, anthers inferior. Female flowers stalk solitary, slender upto15cm long. Underground rhizomes of *Dioscorea* commonly known as wild *yam*. *Dioscorea* has been observed of very high importance in private agencies as well as pharmaceutical firms, and the plant is mainly collected in India along with Himalaya [2, 3]. *Dioscorea* is endangered in natural habitats due to illicit use, spread of cities, and over-use by local peoples for trading and domestic purposes [4]. The species (deltoidea) is mainly found in India, China, Nepal, Bhutan, Pakistan, Afghanistan and Vietnam. In India the plant species are mostly distributed in Kashmir to Assam at altitudes of 550-3100m [5]. In Indian Himalayan regions, it is found in Arunanchal Pradesh, Sikkim, Assam, Meghalaya, Jammu and Kashmir, Himanchal Pradesh, and Uttarakhand [1]. This plant is special because its rhizomes contain Diosgenin, which is a phytoestrogen that convert into the hormone progesterone. Diosgenin is a basis for anti-infertility drugs such as contraceptive pills, and sex hormones, such as testosterone and supplements are used by body builders to increase their testosterone levels and build muscle strength. *Dioscorea* tubers are straight and zinger like shaped. The tubers Of *Dioscorea* are use in the management of a number of diseases such as gastrointestinal disorders, sour throat from struma, diarrhea, irritability, abdominal pain, wounds, burns and anemia. The tubers are also supposed to possess activities like antimicrobial, antioxidant, stomachic and hypoglycemic activities [6]. Besides it, *Dioscorea* is used extensively in the treatment of dysentery, piles and chronic liver pain disease [7].

Classification

- KINGDOM: Plantae
- PHYLUM: Tracheophyta
- ORDER: Dioscoreales
- CLASS: Spermatopsida, Mangolipsida, Monocotyledons
- FAMILY: Dioscoreaceae
- GENUS: Dioscorea
- SPECIES: *D. Deltoidea, D. Bulbifera, L. D. alata.*

Figure 1: Some common *Dioscorea* species. (1) Leaves of *D. pentaphylla* (2) *D. bulbifera* Tubers (3) *D. puber* Tubers (4) *Unequal round winged shaped Seeds of Dioscorea deltoidea* (5) Leaves of *D. puber* (6) Tuber of *different Dioscorea* spp. (7) *D. oppositifolia Flowers,* (8) *D. hispida* Flowers and (9) *D. alata.*

Chemical constituents

Dioscorea rhizomes contain 75% of starch. They are non-edible, due to their very bitter taste. The main constituents of dioscorea are diosgenin, a steroidal sapogenin (4 to 6%) and its glycosides, Smilagenin and β-isomer yammogenin. Rhizomes also contain an enzyme sapogenase. Tubers are also rich in glycosides, and phenolic compounds. Diosgenin is the hydrolytic product of saponin-dioscin [8]. Dioscin is made of two molecules of L-rhamnose and one molecule of D. glucose. Gracillin comprises two molecules of D. glucose and one molecule of L-rhamnose [9]. Ozo.*et al* [10] in 1985 reported flavonoid constituents Cyanidin-3-glucoside and the procyanidin dimmers B-1 and B-3 in *Dioscorea alata* L. A report shows that Dioscorea also contains dioscorins which exhibit carbonic anahydrase and trypsin inhibition activities [11]. Other studies report the presence of saponins, alkaloids, flavonoids, tannin, and phenols in *Dioscorea belophylla* [12]. Also Yoon *et al* [13] in 2008 reported Allantoin, in *Dioscorea* rhizomes.

Table 1: Common bioactive compounds present in *Dioscorea* species.

Compounds	Uses	Species
Diosgenin [14]	Raw material for steroidal drugs	*Dioscorea deltoidea* Wall. ex Griseb.
Sapogenin [15]	Reduce inflammation	*Dioscorea* spp.
Saponin [16]	Skin disease	*Dioscorea* spp.
Cyanidin [11]	Reducing trypsin level	*Dioscorea* spp.
Flavonoids [12]	Antioxidant and skin disease	*Dioscorea belophylla* (Prain) Voigt ex Haines
Allantoin [17]	As detoxifying agent for ammonia	*Dioscorea* spp.
Dioscorine [18]	For Birth control	*Dioscorea bulbifera* L.
Ohenolic compounds [19]	Skin Disease	*Dioscorea pentaphylla* L.

Pharmacological Activity

Anticancer Activity

The treatment of cancer from steroidal compounds is becoming an attractive choice for medicinal chemists and many active molecules have shown this activity [20, 21]. Diosgenin is also investigated to show chemopreventive/therapeutic effect against cancers of several organs, and this has established the high importance of this molecule as a potential antitumor agent [22, 23]. Diosgenin has been tested for anticancer effect in various tumoural cell lines and it was found that the anticancer activity depends on the cell type and on concentration. Thus, diosgenin has antiproliferative activity, for various cancers namely, in prostate cancer (PC-3 and DU-145 cells) [24]. (Colon carcinoma (HCT-116 and HT-29 cells), erythroleukemia (HEL cells), squamous carcinoma (A431, Hep2, and RPMI 2650 cells), hepatocellular carcinoma (HepG2 and HCC cells) [21, 25, 26] gastric cancer (BGC-823 cells), lung cancer (A549 cells) [27] breast cancer (MCF-7), and human chronic myeloid leukaemia (CML) (K562 cells) [28]. Regarding mechanism of action, many studies report that diosgenin is associated with a change of several cell signalling events which are necessary for cell growth/proliferation, differentiation, epithelial-mesenchymal transition migration, and apoptosis, as well as oncogenesis and angiogenesis [30]. Within the various phases of tumorigenesis, Diosgenin is believed to induce apoptotic cell death in various stages of tumorigenesis and thus avoiding their malignant transformation [29, 22, 30]. The antitumor effects of diosgenin have been demonstrated, to occur through p53 activation, immune-modulation, cell cycle arrest, modulation of caspase-3 activity, and activation of the transcription STAT3 signalling pathway [21, 23, 25]. Regarding this perspective, studies have revealed that diosgenin inhibits the production of osteosarcoma cells through the induction of apoptosis and cell cycle arrest in G1 phase [31] and also inhibits the spread of breast cancer cells (MCF-7 cells) by inducing the proapoptotic p53 protein and an improve in caspase-3 levels [21, 32]. Besides it, the propagation of PC-3 human prostate cancer cells is repressed by diosgenin in a depending on the dose. Diosgenin also shows antimetastatic effect by decreasing the cell migration and incursion by diminishing matrix metalloproteinase expression [24]. Diosgenin is studied to have antioxidant activity, due to which it constitutes an interesting approach for lung cancer therapy [27, 33]. The diosgenin-induced apoptosis of human erythroleukemia cell line was associated with increase in number of receptors of Cyclooxygenase-2 [34].

Diosgenin also shows antimetastatic effects in human breast cancer by inhibiting the movement of human breast cancer MDA-MB-231 cells, by partially decreasing Vav2 protein activity [35]. It has been reported that diosgenin reduces the VEGF expression in PC-3 cells, depending on dose, signifying this steroid can inhibit angiogenesis by interfering with this factor [24]. All of the above stated studies have revealed considerably the potential use of diosgenin as a new therapeutic agent against various types of cancer. Therefore, efforts are being made to use the potential of diosgenin as individual drug and with some other bioactive compounds in regulating development and propagation of various types of human tumours and in the study of its potential mechanism of action. An example of this type, the combination of diosgenin and thymoquinone was found to have antiproliferative and apoptotic effects on squamous cell carcinoma (SCC), in a synergistic way, and thus, it could be a novel strategy for the development of potential antineoplastic therapies against squamous cell carcinoma [36]. Diosgenin with other potential drugs tamoxifen is used for the target drug delivery system enclosed in manganese ferrite nanocarriers for enhancing the bioavailability and as a therapeutic tool against breast cancer [37, 38]. Li *et al*. [39] prepared and evaluated diosgenin- polyethylene glycol conjugates as a potential drug delivery system for cancer therapy.

Anti-Infectious Activity

Diosgenin was also examined for its anti-microbial effects, namely, against fungi, bacteria, protozoa, and virus. As for the human pathogens like Candida albicans, C. glabrata, and C. tropicalis, this steroid show weak antimicrobial activity against all the tested organisms [40, 41]. In addition the above organisms, diosgenin also has little to no effect against the fungi like Aspergillus flavus, Aspergillus niger, Trichoderma harzianum, and Fusarium oxysporum. On contrary to this, the sapogenin showed considerable vulnerability against various Gram-positive (Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, and Staphylococcus epidermidis) and many Gram-negative (Escherichia coli and Salmonella typhi) pathogens [42]. Besides, diosgenin has the antiamebic activity against Naegleria fowleri trophozoites at the cellular and molecular levels. Furthermore, it is less toxic to mammalian cells at therapeutic levels than that of amphotericin B, which is currently used to treat N. fowleri infections [43]. In addition, diosgenin shown to be effective in some viral diseases. Diosgenin due to its antioxidant activity can be useful in HIV patients with dementia [44]. Moreover, the steroid exhibits antiviral activity against Hepatitis C Virus (HCV) in *invitro* studies. Diosgenin acts by reducing plasma cholesterol and HCV requires cholesterol for an efficient multiplication that is this shows antiviral effect [45].

Anti-Inflammatory and Immunological Activity

The anti-inflammatory activity of Diosgenin is known to show anti-inflammatory activity however, the mechanism of action is yet uncertain. D.H.Jung *et al*. [46] studied that a diminution in the production of several inflammatory mediators, including NO and interleukins 1 and 6, in murine macrophages which had been pretreated with diosgenin and stimulated with lipopolysaccharide/interferon-*γ*. Moreover, a study in mouse was carried out in which it was evidenced that diosgenin has an inhibitory effect on the production of superoxide generation in bone marrow activated neutrophils and it was observed that this steroid effective and concentration-dependently inhibited the extracellular and intracellular superoxide anion generation. Furthermore, this effect was related with an inhibition of cAMP, PKA, cPLA 2, PAK, Akt, and MAPKs signalling pathways [47]. A study for anti-inflammatory activity in vascular smooth muscle cells (VSMC) was made and it was demonstrated that diosgenin decreased the adhesive capacity of VSMC cells and the Tissue Necrosis Factor (TNF-*α)* mediated induction of intracellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) in VSMC by inhibiting the mitogen-activated protein kinase (MAPK)/protein kinase B (Akt or PKB) signalling pathway and reactive oxygen species (ROS) production [48]. This describes the ability of this compound to curb inflammation within the atherosclerotic lesion and to regulate the immune response. In very recent times, it was investigated that diosgenin modulates adipokine expression in perivascular adipose tissue and improves endothelial dysfunction via regulation of AMPK which can also explain its potential to protect endothelial functions against inflammatory conditions [49]. Besides, it was verified that the in vivo antiallergic activity of diosgenin occurs through inhibition of IgE production, mast cell permeation and degranulation. A recent study shows that the use of diosgenin provides a considerable protection against the monocrotaline-induced pulmonary hypertension in rats. Actually, diosgenin prevents hemodynamic changes and alleviated oxidative stress, inflammatory, and apoptotic markers induced by monocrotaline. This defensive effect could be mediated through preserving eNOS expression together with inhibition of iNOS overexpression [50]. In addition to this, the effect of diosgenin on phthalic anhydride-induced skin inflammation using transgenic mice was studied. The results demonstrated the association of IL-4 (interleukin-4) with inhibition of diosgenin in skin inflammation induced by recurrent dermal exposure to phthalic anhydride [51]. Diosgenin due to its anti-inflammatory and immunomodulating activities could be effective in osteoarthritis-a progressive destruction of articular cartilage and synovial inflammation, In this regard, it was investigated that this steroid inhibits IL-1*β*-induced expression of inflammatory mediators, including metalloproteinase 3 and 13, inducible nitric oxide synthase, and COX-2 in human osteoarthritis chondrocytes [52]. It was also verified that diosgenin improved the expression of VEGF, angiopoietin, and endothelial tyrosine kinase receptor and therefore can be used in rheumatoid arthritis [53].

Diabetes

Various studies show that food sources such as fenugreek seeds and yam tubers containing Diosgenin show anti-diabetic effects in experimental models [54, 55]. Diosgenin, when used streptozotocin-induced diabetic rats notably lowered plasma glucose in comparison to other diabetic controls [56]. Further these reports were supported with the fact that the steroid improves the activity of essential enzymes involved in glucose metabolism altered by diabetes [56].

Besides, studies on lipid accumulation in 3T3-L1 preadipocytes in type 2 diabetic rats have shown that diosgenin (at concentration 0.1 to 10 μmol·L−1) can promote the expression of PPARγ (peroisome proliferative-activated receptor gamma) and the differentiation of adipocyte, which lead to hypolipidemic effect diosgenin [57]. It was found that chronic inflammation in adipose tissue is also a cause of obesity-related insulin resistance and type 2 diabetes [58].

Effect on Cardiovascular System

Various studies indicated that, diosgenin has a considerable effect on lipid levels by reducing the level of total cholesterol (TC) in plasma and Low density lipoproteins (LDL) and increase the ratio of high density lipoproteins (HDL) to total cholesterol by decreasing cholesterol absorption and increasing cholesterol secretion [59]. Diosgenin is found to have concentration dependent vasorelaxant in superior mesenteric rings studied against phenylephrine as a standard. Diosgenin acts by increasing intracellular calcium concentrations in mesenteric endothelial cell loaded with FURA-2. Besides it, nitric oxide (NO) level is also increased by diosgenin [60]. Diosgenin was investigated for vasodilatory effect via porcine resistance left anterior descending coronary artery and it was found that diosgenin through protein kinase G signaling cascade and an opening of BK (Ca) channel of arterial smooth muscle cells caused an acute endothelium-independent coronary artery relaxation [61]. Diosgenin effects were examined in mouse by means of myography and confocal microscopy for contraction of smooth muscle cell and calcium signaling in isolated aorta. Diosgenin was also observed to have a potential therapeutic value for vascular disorders by inhibiting receptor-mediated calcium signals and smooth muscle contraction in the isolated aorta [62].

Effect on Blood System

Diosgenin was investigated to have anti-thrombosis effect in both *in vitro* and *in vivo* studies by using thrombotic rat inferior vena cava and pulmonary thrombosis mice models, it resulted with repressed platelet accumulation, thrombosis and extended activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) in the models depending on dose used. Anti-thrombotic effect of diosgenin is also demonstrated as it increases bleeding time and clotting time [63].

Effect on Central Nervous System

Effect of diosgenin on nervous system was investigated and is reported to have action on potential generation in human cortical neurons (HCN-1A) and big potassium (BK) channel activity improvement was also found. It also increased intracellular Ca^{2+} in human cortical neuronal-1A cells. HCN-1A cells contain alpha- subunit of BK (Ca) – channels seen by Western blotting technique. Therefore, diosgenin may have affect on the activity of cortical neurons by acting on these channels [64]. Further

a study, showed diosgenin significantly affect acetylcholinesterase (AchE) inhibitory activity [65].

Effect on Reproductive System

Diosgenin was investigated on ovariectomized rats and was to found to show effect on the calpain isoform expression in ovariectomized rats. As compared to the normal controls expression of mu- or m-calpain was found to be reduced in the ovariectomized group [66]. Diosgenin was observed to considerably increase the mammary development scores, when studied for its effect on the growth of mammary epithelium for about fifteen days through factors of increase in DNA content, increase in number of ducts and appearance of terminal end buds. Diosgenin and estrogen when used concurrently, showed increase of estrogenic effect of diosgenin particularly at the higher dose level [67].

Diosgenin as a raw material for steroid

There is a three step efficient synthesis for the commercial production of 16-dehydropregnenolone acetate (16-DPA) which is a potent steroid drug intermediate obtained from diosgenin, in an overall yield of 60%. The steps are; acetolysis (isomerisation) of diosgenin 3 to pseudodiosgenin diacetate 4, Oxidation of pseudodiosgenin diacetate 4 to Diosone 5, Hydrolytic degradation of Diosone 5 to 16-DPA 1 [68].

Table 2: Ethnobotanical and medicinal uses of common *Dioscorea* species

Botanical name	Part of Plant	Ethno-botanical/medicinal use
Dioscorea alata L.	Tuber [69]	Treatment of piles
	Tuber [70]	Reduce weakness
	Tuber [71]	Wormicide for stomach worms
Dioscorea belophylla (Prain) Voigtex Haines	Tuber [72]	Taken with hot water is given for the treatment oft fever, malaria, headache, and Dysentery
Dioscorea bulbifera L.	Tuber [73]	Appetitizer.
	Tuber [74, 75, 76, 77]	Analgesic for labour pain, antacid, anti-inflammatory and for treating Dysmenorrhoea.
	Leaves [78]	Skin diseases.
	Tubers [79]	Analgesic for throat pain
	Tubers [80]	Antipyretic.
	Tubers [81]	Treatment of boils and dysentery.
	Tubers [69]	Antidiarrhoeal
	Tubers [82]	Cooling agent
	Tubers [83]	Treatment of skin infection
	Tubers [84]	Anticough and antiseptic
	Tubers [82]	Antaacid and ulcers treatment
	Stem [82]	Antidandruff.
	Tubers [85]	Taken with cow milk for the treatment of cough and Asthma.
	Tubers [86]	Treatment for typhoid when used with *Curcuma aromatica*
	Tubers [87]	Treat ulcer, piles, syphilis, and dysentery, and used to kill hair lice.
	Tubers [70]	Used as contraceptive
	Tubers [87]	Treatment of abdominal pains. and ulcers
	Tubers [80]	Used with salt to cure cough.
Dioscorea dumetorum (Kunth) Pax	Tubers [88]	Poison for arrow heads
	Tubers [88]	Used for treatment of jaundice
Botanical name	Part of Plant	Ethno-botanical/medicinal use
Dioscorea esculenta (Lour.) Burkill	Tuber [88]	Analgesic for chest pain, anti-inflammatory
	Tuber [88]	Treat boils, dysentery and swellings
Dioscorea hamiltonii Hook.f	Tubers [88]	Relieve stomach pain
	Tubers [88]	Appetizer
	Tubers [89]	Refrigerant and Antidiarrhoeal
Dioscorea hirtiflora Benth	Tubers [90]	Used to cure gonorrhea
Dioscorea hispida Dennst	Tubers [91]	Medicine for eyes
	Tubers [92]	Fish poison
	Tubers [89]	Used to treat peeling out of skin
	Tubers [82]	Antiemetic and purgative
	Tubers [70]	Used for healing wounds and injuries
Dioscorea kamoonensis Kunth	Tuber [88]	Treatment of Rheumatoid arthritis
Dioscorea oppositifolia L.	Tuber [94]	Post pregnancy nutrition tonic
	Leaf [89]	Taken with honey to increase sperm

	Tuber [93]	Antiseptic
	Tuber [92]	Used to treat scorpion bite
	Tuber [70]	Used with leaves of clematis to treat seizures or convulsions
Dioscorea pentaphylla L.	Tubers [88]	Reduce swelling of joints and improve immunity
	Tubers [95]	Analgesic for stomach pain
	Tubers [89]	Used to treat sick cattle
	Tubers [82]	Tonic and Spasmodic
	Tubers [70]	Inflorescence is used as vegetables for body weakness
Dioscorea pubera Blume	Bulbils [93]	Relieve colic pain
Dioscorea wallichii Hook.f.	Tubers [82]	Carminative
	Tubers [96]	Analgesic for stomach pain

CONCLUSION

The above study revealed that dioscorea contains various phytochemicals such as Diosgenin, saponin, flavonoids, dioscorin and other important constituents. These chemicals have vast activities like anticancer, antimicrobial, cardiac activities, CNS effects and many more. For this reason, Dioscorea is a potential medicinal plant of interest in the treatment /prevention of several diseases. Diosgenin which is the most identified compound in dioscorea species is a precursor of steroidal drugs as estrogen. Thus it can be said that Dioscorea is a packet which encloses medication for a number health conditions.

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