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# A Comprehensive Phytopharmacological Review of *Dioscorea bulbifera Linn*

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**Abstract**

*Dioscorea bulbifera* Linn. is an important medicinal plant, which has long been used in traditional Indian and Chinese medicine for various diseases. This plant is pharmacologically studied for antitumor, anti HIV, antidyslipidemic, analgesic, anti-inflammatory, diuretic, gastroprotective, antioxidant, antimicrobial, antiviral, antifungal, anthelmintic, neuropharmacological, cardioprotective, anorexiant, plasmid curing activities and anti-hyperthyroid activities. A wide range of phytochemical constituents have been isolated from this plant. A comprehensive account of the morphology, microscopical characters, phytochemical constituents and pharmacological activities reported are included in view of the many recent findings of importance on this plant.

**Keywords:** *Dioscorea bulbifera*; Neuropharmacological activity; Antitumor activity, Diosgenin

**Abbreviations:** CFA: Complete Freunds Adjuvant; LPS: Lipo Poly Saccharides; PLSN: Partial Ligation Sciatic NervE; NOS: Nitric Oxide Synthase; VRE: Vancomycin-Resistant Enterococci; LVDP: Left Ventricular Developed Pressure

## Introduction

Ayurveda is a system of traditional medicine native to India and a form of alternative medicine. Recently traditional medicine worldwide is being re-evaluated by extensive research works on different plant species and their active therapeutic principles. The untapped wealth of plant kingdom can represent a novel source of newer compounds with significant therapeutic activities [1]. One such plant, *Dioscorea bulbifera* Linn, which have various medicinal properties, is widely used in Ayurveda, the ancient traditional medicinal system in India. *Dioscorea bulbifera* is an aerial yam commonly known as Varahikanda. In this review a comprehensive account of the morphology, microscopical characters, phytochemical constituents and pharmacological activities are included in view of the many recent findings of importance on this plant.

## Taxonomic Classification [2]

Kingdom: Plantae

Subkingdom: Viridaeplantae

Superdivision: Streptophyta

Division: Tracheophyta

Class: Magnoliopsida

Superorder: Lilinanae

Order: Dioscoreales

Family: Dioscoreaceae

Genus: Discorea L.

Species: *Dioscorea bulbifera* L.

## Vernacular Names [3,4]

English: Potato Yam, Air potato

Sanskrit: Varahikanda, Aluka, Shukara

Hindi: Varahi kanda, Kadu Kanda, Ratalu

Gujarati: Dukkarkanda

Bengali: Ratalu, Ban Alu

Tamil: Kodikilanga, Kaattu-k-kaay-valli

Marathi: Manakund, Kadu-karanda, Varahi

Kannada: Kuntagenasu

Konkani : Karamdo

Malayalam: Pannikizhangu, Kattukachil

Oriya: Pita Alu

Telugu: Adavi Dumpa

### Synonyms

*D. crispate* Roxb, *D. pulchella* Roxb, *D. sativa* sensu Hook.f [3,4].

### Ayurvedic Preparations

Ajamamsa Rasayanam, Narasimha Churna, Pancha Nimbadi Churna, Vastyamayantaka Ghrita, Varahytadighurdam [3,4].

### Substitute

Varahikanda is used as substitute for Riddhi and Vriddhi drugs of Astavarya in Ayurveda [3,4].

### Occurrence and Distribution

The species is native to the tropics of the old world and occurs in rain forests extending from the west coast of Africa to the farthest island in the specific. It is common throughout India ascending up to 6,000 ft. in the Himalayas. It does not thrive in the dried part of the India. The wild form also occurs in South East Asia, West Africa, South, and Central America, Australia, Louisiana, Texas, Hawaii, Puerto Rico, Polynesia, and Florida [3, 5,6].

### Flowers

September-November

### Fruit

December onwards

### Parts Used

Tubers, Bulbils, Roots,

## Morphology

*Dioscorea bulbifera* is a vigorously twining, long-stemmed perennial vine with non-spiny stems to 20 m or more in length, freely branching above; internodes round or slightly angled in cross section and they twine counter-clockwise. Plant has two types of storage organs. The plant forms bulbils in the leaf axils of the twining stems, and tubers beneath the ground. Tubers are like small, oblong potatoes with bitter taste. Conspicuous aerial tubers (called bulbils) are pale, round to globose in shape, up to 13 cm wide and in inflorescence that give *D. bulbifera* the common name "air potato." The leaves are attractive, alternate, broadly heart-shaped, attached by long petioles. Leaves 10-15 x 7.5-10 cm, ovate-suborbicular, base deeply cordate, apex acuminate to shortly caudate, membranous, glabrous, basally 9-11-ribbed; petiole to 20 cm long. They are divided longitudinally into lobes by prominent arching veins all radiating out from a single point of origin where the petiole attaches to the leaf. Flowers rarely occur in D. bulbifera; where occurring, they are small, pale green and fragrant, and arising from leaf axils. Male flowers in slender, axillary panicled spikes, pendulous, to 18 cm long; bracteoles ovate, acute [5,6].

Perianth light green; lobes 6, biseriate, 2.5 mm long, linear-oblong. Stamens 6 free. Female spikes 1-3 together; staminodes 3; ovary triquetrous, 3-locular, ovules 2-per locule; styles 3; stigma 2-fid, reflexed. Capsules 1.5-2.3 x 1-1.5 cm, oblong, 3-winged. The fruit is a capsule and the seeds partially winged. This species reproduces sexually by seeds and vegetatively by underground and aerial tubers (bulbils) which enable it to spread rapidly and colonize entire forests in a single growing season. The aerial stems of air potato die back in winter season, but resprouting occurs from bulbils and underground tubers.

### Morphology of Bulbils and Tumors

**Figure 1.**

The bulbil is fairly hard and heavy. Dish shaped with to 12 cm (5") x 10 cm (4") brown with prominent numerous, uniformly distributed tubercle like eyes. Bulbils abundant and of different sizes and shapes; in certain cultigens the tuber is suppressed in favour of rather large bulbils, having all the reserve food; small bulbils are, as a rule warted, but they may be smooth when large. Tubers are usually small and round, but large under cultivation. They are weighing up to 1 kg. Tubers are toxic or edible according to the variety; they are renewed annually. Their skin is purplish black or earth colored, usually coated with abundant small feeding roots, but smooth in some cultivated varieties having flesh of white to lemon yellow, sometimes marked with purple flecks and very mucilaginous (Figure 1) A few root and root scars present in tubers, outer surface dark brown, inner yellow to light brown; odour- indistinct; taste-bitter [5,6].

### Microscopic Characteristics

Subasini, 2013 reported microscopic features of tubers and bulbil of *D. bulbifera*. The T.S of tubers showed wide, well developed periderm, vascular bundles and triangular starch grains. Major microscopic characters of bulb include periderm, ground tissue, vascular bundle, and triangular starch grains. Ground tissue, forming major portion of bulb composed of oval to polygonal cells having a few scattered closed vascular bundles. Starch grains found both in cortex and ground tissues, but abundant in ground tissue, rounded to oval, three sided with rounded angles or rod-shaped, simple, solitary or in groups, 11-28 µ in diameter; hilum present at the narrower extremity [7].

### Phytochemical Constituents

Phytochemical analysis of *Dioscorea bulbifera* revealed presence of alkaloids, glycosides, proteins, fats, sterols, alkaloids, polyphenols and tannins, flavonoids and saponins which may


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vary according to country origin [7]. Inorganic micronutrients present include Fe, Cu, Zn, Mn, Co, Mo, V, B, Cl, I, Br and Na [7].

a) Steroidal Saponins [8]: Dioscoreanoside A-K, Dioscoreanoside B, Dioscoreanoside C, Dioscoreanoside D, Dioscoreanoside E, Dioscoreanoside F, Dioscoreanoside G, Dioscoreanoside H, Dioscoreanoside I, Dioscoreanoside J, Dioscoreanoside K, Dioscin

b) Steroidal Sapogenin, Spirostane Glycosides, Cholestane Glycosides [9-11]: Diosbulbisin A, Diosbulbisin B, Diosbulbisin C, Diosbulbisin D, Diosbulbisides A, Diosbulbisides B, Diosbulbisides C, Diosgenin, Sinodiosgenin

c) PNorclerodane Diterpenoids [12-16]: Diosbulbin A, Diosbulbin B, Diosbulbin C, Diosbulbin D, Diosbulbin E, Diosbulbin F, Diosbulbin G, Diosbulbin H, Diosbulbin I, Diosbulbin J, Diosbulbin K, Diosbulbin L, Diosbulbin M, Diosbulbin N, Diosbulbin O, Diosbulbin P, 8-Epidiosbulbin E Acetate

d) Clerodane Diterpenoids [17-19]: Bafoudiosbulbin A, Bafoudiosbulbin B, Bafoudiosbulbin C, Bafoudiosbulbin F, Bafoudiosbulbin G.

e) Flavanoids Derivatives [20,21]: Quercetin-3-O-β-d-glucopyranoside, Quercetin-3-O-β-d-galactopyranoside, Myricetin-3-O- β-D-galactopyranoside, Myricetin-3-O-β-D glucopyranoside, 3,5-dimethoxy-kaempferol, 3, 5, 3′-trimethoxyquercetin, Caryatin, Hyperoside, Kaempferol, Kaempferol-3-O-β-D-galactopyranoside, Kaempferol-3-O-β-D-glucopyranoside, Kaempferol-3,5-dimethyl ether, Quercetin-3-O-galactopyranoside, Myricetin, Isoquercitrin, Lutein, Quercetin-3-O-β-D-glucopyranoside, 7-bis-(4-hydroxyphenyl) -4E, 6E- heptadien-3-one, 5,3,4-trihydroxy-3,7- dimethoxyflavone.

f) Phenanthrenes [20-22]: 2,7-dihydroxy-4-methoxyphenanthrene, 2,7-dihydroxy-3,4,6-trimethoxyphenanthrene, 1,6-dihydroxy-2,5,7-trimethoxyphenanthrene

g) Carotenoids [3]: Neoxanthin, Auroxanthin, Violaxanthin, Cryptoxanthine

h) Phytosterols [14,18,20]: Daucosterol, β-sitosterol, 3-O-β-D-glucopyranosyl-b-sitosterol, Stigmasterol

i) fatty acids [11,18,22]: Palmatic acid, Succinic acid, Shikimic acid, Tetracosanoic acid, 1-(tetracosanoyl)-glycerol, Trans-tetracosanylferulate, Mono-arachidin, C22 ω-hydroxy fatty acid, 3-hydroxy-5-methoxybenzoic acid, Batatasin III, Behenic acid, Ethyl ester of undecanoic acid, Z-1,9-dodecadiene (C H), n-Hexadecanoic acid, Ethyl ester of Eicosanoic acid

j) Tannins [20,22]: Catechin, Protocatechuic acid, (+) Epicatechin, (-)Epicatechin

k) Volatile oils [20,23] : Vanillic acid, Isovanillic acid

l) Glycoside Derivatives [9,12,15, 24]: Alkaloid [25]: Dihydrodioscorine a) Methyl-O-α-D-fructofuranoside, Butyl-O-α-D-fructofuranoside, Ethyl-O-β-D-fructopyranoside, Butyl-O-β-D-fructopyranoside, 3-phenyl-2-propenyl-O-β-D-glucopyranoside, 2-(4-methoxyphenyl)-ethyl-O-β-D-glucopyranoside, Phenyl -methyl-O-β-D-glucopyranoside. Pennogenin, Pennogenin-3-O-α-Lrhamnopyranosyl-(1→3)-[α-L-rhamnopyranosyl-(1→2)]- β-D- glucopyranoside, Pennogenin-3-O-α-Lrhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]- β-D- glucopyranoside, 3-O-α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→3)]-β-D-g1ucopyranosyl pennogenin (spiroconazol A), 26-O-β-D-glucopyranosyl-(25R)- 5-en-furost-3β,17α,22α,26-tetraol- 3-O-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl- (1→4)-[α-L-rhamnopyranosyl- (1→2)]-β-D-glucopyranoside, 23β,27-dihydroxy-pennogenin 3- O-α-L-hamnopyranosyl-(1→4)- α-L-rhamnopyranosyl-(1→4)-[α-L-mnopyranosyl-(1→2)]-β-Dglucopyranoside, 4-hydroxy-[2-trans-3′,7′- dimethylocta-2′,6′-dienyl]-6-methoxy acetophenone, 4,6-dihydroxy-2-O-(4′- hydroxybutyl) acetophenone, Diosbulbinoside D, Diosbulbinoside F, Diosbulbinoside G

m) Others [15,26]: Demethyl batatasin IV, Diarylheptanone, 3,5,4′-trihydroxy-3′- methoxybibenzy, 1,7-bis-(4-hydroxyphenyl)- 1E,4E,6E-heptatrien-3-one, 2,3′-di-hydroxy-4′,5′- dimethoxybibenzy, Docosyl ferulate, Tristin, Adenosine.

## Reported Pharmacological Activities

### Antitumour Activity

It has been reported that the extraction of components from *D. bulbifera* using organic solvents of little polarity significantly inhibited the growth of tumor and prolonged the survival of tumor-bearing mice and human liver cancer, colon cancer and other tumor cells [27-31]. *D. bulbifera* decoction could inhibit cell growth in the human squamous cell carcinoma cell line SiHa, in the human cervical cancer cells Hela, and in the human hepatoma cells HepG2, in a dosage and time-dependent manner [32]. Komori found that diosbulbins A and B had remarkable growth inhibition effect on solid sarcoma180 tumor cells [12]. Another study reported the anti-tumour-promoting effect of 75 % ethanol extracts of the rhizomes of *Dioscorea bulbifera* L. using the neoplastic transformation assay of mouse epidermal JB6 cell lines.

The ethyl acetate and n-butanol soluble fractions showed different inhibitory activities against tumour promotion of JB6 (Cl 22 and Cl 41) cells induced by the promoter of 12-O-tetradecanoylphorbol-13-acetate (TPA) [20]. Kaempferol-3,5-dimethyl ether, caryatin, (1)-catechin, myricetin, quercetin-3-O- galactopyranoside, myricetin-3-O-galactopyranoside, myricetin-3-O-glucopyranoside and diosbulbin B isolated


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from ethyl acetate soluble fraction of 75 % ethanol extract of the rhizomes of *Dioscorea bulbifera* L. from China showed an antitumor-promoting effect against the neoplastic transformation assay of mouse epidermal JB6 cell lines [21]. Petroleum ether fraction from chinese Dioscrea bulbifera showed potential effects against microstructure abnormality of HepA cells surface [33]. Two new steroidal saponins, diosbulbisides D (1) and E (2), along with five known saponins (3- 7) were isolated from the rhizomes of *Dioscorea bulbifera* L. Compounds 6 and 7, two 3- O-trisaccharides of diosgenin spirostanes, showed moderate cytotoxic activity against human hepatocellular carcinoma cells, with $IC_{50}$ values of 3.89 μM and 7.47 μM on SMMC7721, and 10.87 μM and 19.10 μM on Bel-7402 cell lines, respectively [34].

**Table 1:** Traditional uses [27-30].

| Place | Medicinal uses |
|---|---|
| India | It is a prime staple medicinal-food substitute for the majority of rural and local people of the state of India. The rural and local people who use them as food supplements make them edible by different traditional practices. Tubers are mostly soaked overnight in water or left overnight in stream and subjected to successive boiling to remove the bitterness. Tubers are roasted, cooked as vegetable. Shushruta mentioned it as Rasayana. Tuber powder prescribed with honey and milk for anti aging effect and causes cell and tissue rejuvenation. It improves sperm and semen quantity and quality and used for impotency and infertility, as Male/female reproductive tonic. It also improves voice, digestion, strength and immunity with balancing Kapha and Vata. Tubers are used in leprosy, asthma, cough, cold, tuberculosis, contraceptive, constipation, indigestion, abdominal pain, muscular pain, bone fracture, dysentery, sore throat, struma, wounds, boils, cuts, injury, carbuncle, tumour and also used as refrigerant to reduce body heat during summer. Tubers are also used for the treatment of purgative, deflatulent, aphrodisiac, rejuvenating and tonic anthelmentic, haemorrhoids, scrofula, worm infestations, general debility and polyuric. Fresh tuber decoction cures laryngitis in children, insect bite, ring worm, goitre, and fever. Root powder is used as component of local medicine for tuberculosis. It maintains kidney function. Also used in diseases of lungs, spleen, diarrhoea, improving digestion and metabolism. Bulbils cure typhoid of children. |
| Bangladesh | Tubers are used for treatment of leprosy and tumours. |
| China | Tubers are used for sore throat, struma, dog bites, snake bites, food poisoning, hepatic fibrosis, gastric cancer and carcinoma of rectum, and goiter. |
| Zimbabwe | Tubers are applied on cuts and sores as infusion. |
| Java, Brazil | Tubers are used in dysentery, diarrhoea and syphilis. |
| Latin America | Tubers are used treat diarrhoea, dysentery, conjunctivitis, fatigue and depression among other ailments. |
| Africa | Bulbils as hunting poison and tubers as fishing poison. External application as a medication for skin disease, boils and ulcers as well as lice and rheumatism. |
| Zaire | Apply a grilled leaf with little palm oil to an infected wound. |
| Tanzania | Tubers are used leaves for eye steam bath. |
| Congo | Plant juice is drunk as a medication for snakebite and suppurating eye inflammation. |
| Benin | The leaf juice is give orally in case of difficult birth. |
| Cameroon | Decoctions of pseudobulbs are used for hookworm and mawwarm and the scrapping of bulbils as a poultice for treatment of abscesses, boils and wound infections. |
| Madagascar | Pulp of pounded bulbils for treatment of abscesses, boils and wound infections. |

The results of antitumour activity of water extract (fraction A), ethanol extract (fraction B), ethyl acetate extract (fraction C), non-ethyl acetate extract (fraction D) and isolated diosbulbin B showed that fractions B and C both decreased tumour weight in S180 and H22 tumour cells bearing mice, while fractions A and D had no such effect. Furthermore, fraction C altered the weight of spleen and thymus, and the amounts of total leukocytes, lymphocytes and neutrophils in tumour-bearing mice. Diosbulbin B was found to be the major antitumor bioactive component in the extracts and demonstrated anti-tumor effects in the dose-dependent manner at the dosage of 2 to 16 mg/kg without significant toxicity in vivo [35].

Immune system modulation might be related to antitumor effects of *D. bulbifera* rhizome, as reported in S180 and H22 tumor cells bearing mice [35]. Alcoholic extracts (70%, 80% and 90% alcohol) of *D. bulbifera* were found to in hibited the proliferation of human gastric cancer cell line SGC-7901 [36]. Zhao 2012 proved that *D. bulbifera* could significantly decrease the expression of SW579 Survivin mRNA and protein in human thyroid cancer cells and also induce apoptosis of cancer cells [37,38]. Pennogenin- 3-O-a-L-rhamnopyranosyl-(1 → 3)-[a-L-rhamnopyranosyl-(1→ 2)]-b-D-glucopyranoside and Pennogenin-3-O-a-L-rhamnopyranosyl-(1 → 4)-[a-L-rhamnopyranosyl-(1→2)]-b-D-glucopyranoside from *D. bulbifera* extract showed significant cytotoxic activity against the proliferation of Bel-7402 human hepatocellular carcinoma cells, with 99.1 and 92.6% inhibition, respectively.

Both compounds showed cell growth inhibition activity toward SMMC7721 human hepatocellular carcinoma cells of 4.54 and 4.85 lM respectively [9]. Spiroconazol A and Pennogenin-


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3-O-a-L-rhamnopyranosyl-(1→ 4)-a- L-rhamnopyranosyl-(1→ 4)-[a-L-rhamnopyranosyl- (1→2)]-b-D-glucopyranoside showed moderate cytotoxicity against ECV304 urinary bladder carcinoma cells, by membrane toxicity via lactic dehydrogenase (LDH) liberation with IC50 values of 8.5 lg/ml (8.3 lM) and 5.8 lg/ml (6.6 lM), respectively. 26-O-b-D-Glucopyranosyl-(25R)-5-en-furost-3b,17a,22a,26-tetraol-3-Oa-L-rhamnopyranosyl-(1→4)-a-L-rhamnopyranosyl- (1 → 4)-[a-L-rhamnopyranosyl-(1 → 2)]-b-D-glucopyranoside showed moderate activity as well, by a direct influence on the mitochondrial metabolism without liberation of LDH with an IC50 value of 14.3 lg/ml [38]. Combination of *D. bulbifera* polysaccharides and Cyclophosphamide could potentially enhance the anti-tumor effect of Cyclophosphamide and attenuate Cyclophosphamide induced immunosuppression as well as oxidative stress in U14 cervical tumor-bearing mice [39]. Platinum–palladium bimetallic nanoparticles of *Dioscorea bulbifera* tuber extract showed anticancer activity against HeLa cells [40].

## Anti HIV Activity

Anti-HIV-1 integrase activity was evaluated for 7 compounds isolated from ethyl acetate and water fractions of *Dioscorea bulbifera* bulbils. Flavanoid Myricetin exhibited the most potent anti-HIV-1 integrase activity (IC50 value of 3.15 mM) followed by 2,4,6,7-tetrahydroxy- 9,10-dihydrophenanthrene (IC50 value¼14.20 mM), quercetin-3-O-b-D-glucopyranoside (IC50 value¼19.39 mM) and quercetin-3-O-b-D-galactopyranoside (IC50 value¼21.80 mM). Potential interactions of the active compounds with the IN active site were additionally investigated. These compounds interacted with Asp64, Thr66, His67, Glu92, Asp116, Gln148, Glu152, Asn155, and Lys159, which are involved in both the 3'-processing and strand transfer reactions of integrase enzyme [41,42].

## Antidiabetic Activity

Aqueous extract of *D. bulbifera* tubers at 250, 500 and 1000 mg/kg doses administered for 3 weeks to glucose primed and streptozotocin induced diabetes in wistar rats treated rats showed significant antihyperglycemic activity [42]. Ethanolic extract of *Dioscorea bulbifera* (aerial yam) was studied against alloxan-induced diabetic rats. Intraperitoneal administration of a single dose of 380.0, 760.0 and 1140.0 mg/kg body weight of the extract were exhibited significant reduction in the blood glucose levels of the albino rats [43]. One study reported that among petroleum ether, ethyl acetate, methanol and 70% ethanol (v/v) extracts of bulbs of D. bulbifera, ethyl acetate extract showed highest inhibition upto 72.06 ± 0.51% and 82.64 ± 2.32% against α-amylase and α-glucosidase respectively. Diosgenin was isolated showed a α-amylase and α-glucosidase inhibition upto 70.94 ± 1.24% and 81.71 ± 3.39%, respectively by interacting with two catalytic residues (Asp352 and Glu411) from α-glucosidase [44]. Copper nanoparticles synthesized by *D. bulbifera* tuber extract also showed significant inhibition against α-glucosidase and murine intestinal glucosidase [45].

## Antidyslipidemic Activity

Aqueous extract of *D. bulbifera* tubers at 250, 500 and 1000 mg/kg doses administered for 4 weeks to high fat diet fed C57BL/6J mice showed significant antidyslipidemic effects [42].

## Analgesic and Anti-Inflammatory Activities

The aqueous and methanol extracts from the dry bulbils of *Dioscorea bulbifera* L. var sativa were evaluated (300 and 600 mg/kg, p.o.) against pain induced by acetic acid, formalin, pressure and against inflammation induced by carrageenan, histamine, serotonin and formalin in experimental animals. The results showed potent analgesic and anti-inflammatory activities of the extracts which may be due to inhibition of inflammatory mediators such as histamine, serotonin and prostaglandins [46]. Antiinflammatory activity of ethanol extract of *Dioscorea bulbifera* leaf (500 mg/kg, 250 mg/kg, 125mg/kg, 62.5mg/kg, 31.25mg/kg, 15mg/kg p.o.) was reported against egg albumin induced rat paw oedema [47]. Diosbulbin B from *D. bulbifera* had inhibitory effects on both acute and subacute inflammation [48]. The effects of methanol extract of the bulb of *Dioscorea bulbifera* var sativa (250 and 500 mg/kg, p. o.) were tested in mechanical hypernociception induced by intraplantar injection of complete Freund's adjuvant (CFA), lipopolysaccharides (LPS) or prostaglandin-E2 (PGE2), as well as in partial ligation sciatic nerve (PLSN), nociception induced by capsaicin and thermal hyperalgesia induced by intraplantar injection of CFA. The therapeutic effects of *Dioscorea bulbifera* on PGE2-induced hyperalgesia were evaluated in the absence and in the presence of L-NAME, an inhibitor of nitric oxide synthase (NOS) and glibenclamide, an inhibitor of ATP-sensitive potassium channels. The extract showed significant antinociceptive effects in persistent pain induced by CFA and on neuropathic pain induced by PLSN. *D. bulbifera* significantly inhibited acute LPS-induced pain and PGE2 induced pain. The results showed the mechanism of antinociceptive activities of *D. bulbifera* in both inflammatory and neuropathic pain may be the activation of the NO-cGMP-ATP-sensitive potassium channels pathway [49]. Methanol extract of *D. bulbifera* could inhibit the nitric oxide production and iNOS mRNA expression of LPS-induced macrophages in vitro, which may be one of the mechanisms of its anti-inflammatory action [50].

## Diuretic Activity

Diuretic activity of ethanol extract of *Dioscorea bulbifera* leaf (500 mg/kg, 250 mg/kg, 125mg/kg, 62.5mg/kg, 31.25mg/kg, 15mg/kg p.o.) was reported in rats [47].

## Gastro Protective Activity

Gastroprotective activity of hydroalcoholic extract of *D. bulbifera* tubers (doses of 100, 200 and 400 mg/kg) was reported against indomethacin-induced gastric ulcers in rats [51].

## Antioxidant Activity

Hydroalcoholic extract of *D. bulbifera* tubers (doses of 100, 200 and 400 mg/kg) reversed the indomethacin induced gastric


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ulcers associated free radical changes and showed antioxidant activity by inducing a significant increase of peroxidase and catalase while reduction in glutathione peroxidase, reduced glutathione, and lipid peroxidation level in tissues [51]. Scavenging activity of sequential extracts (petroleum ether, ethyl acetate, methanol and ethanol (70%) of *D. bulbifera* bulbs were checked against pulse radiolysis generated ABTS+ and OH radical, in addition to DPPH, superoxide and hydroxyl radicals by biochemical methods. Ethyl acetate extract of *D. bulbifera* bulbs which contain diosgenin as a major constituents exhibited excellent scavenging pulse radiolysis generated ABTS•+ and OH radical [52]. 70% and 80% alcoholic extracts of D.bulbifera showed significant antioxidant activity against hydroxyl radical scavenging test, reducing capacity test and total antioxidant capacity test [36]. Ethanol extract of tubers of *D. bulbifera* also showed antioxidant activity in enzymatic assays (glutathione peroxidase, catalase, superoxide dismutase, glucose-6-phosphate dehydrogenase and glucose-s-transferase) and non enzymatic assay (reduced glutathione, vitamin C and vitamin E) [53]. Copper nanoparticles synthesized by *D. bulbifera* tuber extract also showed significant scavenging activity against DPPH, nitric oxide and superoxide radicals respectively [45].

## Effects on Immune Systems

Immune function of mice were studied after oral administration of decoction of *D. bulbifera* (1000, 490, 240 g/kg body weight) for 15 days. Results showed that in the high dose group could significantly suppress the phagocytosis activity of mononuclear macrophages. However, the medium dose group markedly enhanced the activities of natural killer cells, the antibody quantity of B cells and the quantity and proliferation of spleen T lymphocytes. This experiment indicated that high doses of *D. bulbifera* could suppress the immune function in mice, while medium doses could improve the immune function [54]. *Dioscorea bulbifera* polysaccharides (100 or 150mg/kg) lowered peripheral blood T-cell subpopulation CD4+/CD8+ ratio, and *Dioscorea bulbifera* polysaccharides + Cyclophosphamide combination attenuated Cyclophosphamide effect in lifting CD4+/CD8+ ratio [55].

## Antimicrobial Activity

Acetone extract, ethyl acetate extract, 95% ethanol extract and methanol extract of *D. bulbifera* each showed a fair antibacterial activity on inhibition of bacteria isolated from animals and poultries using disc method. The acetone extract showed the most significant anti-bacterial effect when compared to other extracts [56]. Aqueous extract of *D. bulbifera* showed superior anti-bacterial activity on E. coli while the anti-bacterial effect of an ethanol extract of *D. bulbifera* was potent against *S. aureus* and *Candida albicans* when tested using disc-diffusion method of antimicrobial assay [57,58]. The methanol extract, fractions (DBB1 and DBB2) and six compounds isolated from the bulbils of D. bulbifera, namely bafoudiosbulbins A (1), B (2), C (3), F (4), G (5) and 2,7-dihydroxy-4-methoxyphenanthrene (6), were tested for their antimicrobial activities against *Mycobacteria* and gram-negative bacteria involving multidrug resistant (MDR) phenotypes expressing active efflux pumps using microplate alamar blue assay and the broth microdilution methods. The good activities of the crude extract, fractions and compound 3 on most of the tested microorganisms belonging to MDR phenotypes such as *E.coli* AG102, *P. aeruginosa* PA124, *E. aerogenes* CM64, *K. pneumoniae* KP55 and KP63 as observed [58]. Two clerodane diterpenoids, Bafoudiosbulbins A and Bafoudiosbulbins B showed significant activities against *P. aeruginosa, S. typhi, S. paratyphi A* and *S. paratyphi B* [59]. 8-epidiosbulbin E acetate showed broad-spectrum plasmid-curing activity against MDR bacteria, including Vancomycin-resistant enterococci (VRE). It cured antibiotic resistance plasmids from clinical isolates, including *Enterococcus faecalis, E. coli, Shigella sonnei, P. aeruginosa* and *Bacillus subtilis* with 12-48% curing efficiency [60]. In addition, vanillic acid and isovanillic acid showed anti-bacterial activities as well [61].

The successive extracts of bulbils of *Dioscorea bulbifera* (bulbils) was investigated for *in vitro* antimicrobial activity. Among all extracts, the petroleum ether and chloroform extracts showed significant activity against *A. fumigatus* and *R. nigricans*. The petroleum ether and distilled water extract showed good activity against *K. pneumoniae*. The chloroform extract showed feeble activity against *S. aureus* [62]. Beta-lactam (piperacillin) and macrolide (erythromycin) antibiotics showed synergistic effect with silver nanoparticles of *D. bulbifera* tuber extract against multidrug-resistant *Acinetobacter baumannii*. Chloramphenicol or Vancomycin also showed synergistic effect with silver nanoparticles of *D. bulbifera* tuber extract against *Pseudomonas aeruginosa*. Streptomycin combined with silver nanoparticles showed strong evidence for the synergistic action against E. coli [63].

## Anti-Viral Activity

The alcohol extract of *D. bulbifera* (0.017–0.034 mg/ml) reported to kill DNA virus and inhibit the transcription of RNA virus in direct or indirect inhibitory experiments. From different parts of the ethanol extracts of *D. bulbifera* (butanol fraction, ethyl acetate fraction, acetone and ether fraction), the inhibition effect of butanol and ethyl acetate fraction on Coxsackie B I–VI virus was better than that of the other two fractions. But their effects on herpes simplex virus I were nearly the same. After killing the virus, the cells still could continue to divide and be subcultured which was indicating that the drug is non-toxic and effective. But the decoction of *D. bulbifera* had no inhibitory effect on various types of viruses [64].

## Antifungal Activity

The decoction of *D. bulbifera* (1:3 ratio of *D. bulbifera* to water) had different degrees of inhibitory effects on a variety of skin fungi, such as Trichophyton violaceum, T. concentricum and T. schoenleinii [65]. It has been proved that the isolated dihydrodioscorine from *D. bulbifera* at 0.1% concentration could


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inhibit the growth of fungi which could cause diseases in several types of plants [25].

### Anthelmentic Activity

Methanolic extracts of the flesh and peel of the bulbils of D. bulbifera, showed *in vitro* anthelmintic activity on *Fasciola gigantica* and *Pheritima posthuma* at concentrations ranging from 10 to 100 mg/ml [66].

### Neuropharmacological Activity

Central nervous depressant action of acute treatment of hydroalcoholic extract of tuber of *Dioscorea bulbifera* (100 and 300 mg/kg, p.o.) was observed as treatments significantly reduced spontaneous motor activity, rectal temperature and prolonged the pentobarbitone induced hypnosis in mice. However, no effect on motor co-ordination as determined by the rota rod test which confirmed central action rather than peripheral action of extract. Further extract treatments also showed anxiolytic activity in plus maze test and head-dip test [67].

### Cardioprotective Activity

Myricetin, epicatechin, isovanilic acid and vanillic acid were shown to be important bioactive components in *D. bulbifera* that protect against cardiovascular diseases [68]. In another study, administration of 70% ethanolic extract of *D. bulbifera* to rats (150 mg/ kg of body weight, 30 days) resulted in significantly improved ventricular performance in terms of aortic flow, left ventricular developed pressure (LVDP) and the first derivative of developed pressure (LVmax dp/ dt) of *D. bulbifera* treated during post-ischemic reperfusion. *D. bulbifera* also significantly reduced the size of myocardial infarction by 20 ± 2.64% as compared to the control group.

The decreased number of apoptotic cardiomyocytes by 16.89 ± 1.7% revealed that *D. bulbifera* had anti-apoptotic activity. The modulation of pro- and anti-apoptotic proteins by *D. bulbifera* was also examined. The upregulation of procaspase 3 and downregulation of cleaved caspase 3 coupled with prevention of loss of phase II enzyme HO-1 suggested that *D. bulbifera* extract ameliorates rat myocardial ischemia and reperfusion injury with an associated reduction in apoptotic cell death [69].

Cardioprotective action of steroidal saponin Diosgenin, isolated from *Dioscorea bulbifera*, was reported against Hypoxia-reoxygenation Injury in H9c2 cardiomyoblast cells as evidenced from the improved cell survival after hypoxia-reoxygenation injury, decreased release of lactate dehydrogenase, during cell death, upregulated the pro-survival molecules like B-cell lymphoma 2 (Bcl-2), heme oxygenase-1 and the phosphorylation of ATK (at serine 473); and at the same time down regulated pro-death molecules like Bax [70].

### Effects on Thyroid Glands

*D. bulbifera* had achieved good effect in the treatment of subacute thyroiditis [71]. In another study, thyroxine (T4) concentration and triiodothyronine (T3)-uptake level decreased in Sprague-Dawley (SD) rats treated with sodium levothyroxine (160 lg/kg, 5 days) and extract of *D. bulbifera* (0.75 or 1.5 g/kg). The results suggested that *D. bulbifera* decreased excess thyroid hormone and increased metabolism, resulting in improvement of the hyperthyroid state [72].

### Anorexiant Activity

Anorexient activity of *Dioscorea bulbifera* Linn Was reported [73].

### Toxicity Study

Acute, subacute and chronic toxicity study of *D. bulbifera* showed that for mice the intraperitoneal LD50 was 25.49 g/kg and the oral LD50 was 79.98 g/kg. The toxicity was mainly manifested as damage to liver and kidney. The degree of damage was related to the dose and time of drug administration [74]. Dioscin and diosbulbin B, derived from Chinese *D. bulbifera* roots (Huang-yao-zi) are responsible for liver toxicities, nausea, abdominal pain, coma and even death.

The mechanism of hepatotoxicity is relevant to its inhibition of antioxidant enzymes in liver mitochondria and the activity of drug metabolic enzymes, such as glutathione transferase, glutathione peroxidase, superoxide dismutase, glucose-6-phosphate and succinodehydrogenase [75-77]. Genetic studies found that the expression of the bad gene was increased in hepatocytes that promoted the apoptosis of mitochondria and endoplasmic reticulum lead to death of hepatocytes [78]. Various other studies support that hepatotoxicity of *D. bulbifera* with methanol extract and its cholorform fraction [79,80] ethyl acetate fraction of 75% ethanolic extract and isolated diosbulbin D [80], diosbulbin B were observed [81]. Another study further confirmed the hepatotoxic effects induced by *D. bulbifera* using molecular function analysis of the changed metabolites including elevated levels of taurine, creatine, betaine, dimethylglycine, acetate and glycine, and decreased levels of succinate, 2-oxoglutarate, citrate, hippurate and urea [82].

8-Epidiosbulbin E from *D. bulbifera* has been reported to cause hepatotoxicity as electrophilic intermediate generated by the metabolic activation of furan ring of 8-Epidiosbulbin E acetate mediated by cytochromes P450 is responsible for liver injury [83]. Various studies also reported renal toxicity of *D. bulbifera* [74,77, 84]. The renal lesions mainly are cloudy swelling of renal tubular epithelial cells, luminal stenosis, and protein casts in renal tubes [74]. Direct cytotoxicity on glomerular and tubular cells, and acute tubular injury was caused by severe parenchymal liver injury [84].

One study reported that *D. bulbifera* also affects the function of the gastrointestinal system. 19.9, 8, 2.7 g/kg of 200% decoction of *D. bulbifera* reported a high degree of gastrointestinal flatulence and congestion of the gastrointestinal vascular system in the dead mice. Pylorus ulcers in the stomach were also visible. Under a light microscope, superficial necrosis of gastric mucosa


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was observed [77]. *D. bulbifera* administration for long term can lead to increased thyroid masses with larger follicular diameters, thick colloid filling in their cavities and flattened follicles in mice and rats. These toxic reactions could be seen in diffuse colloid goiter, which is very similar to the symptoms of goiter induced by iodine poisoning [85].

## Methods of Detoxifications

Major toxicity materials observed are saponins and sapogenins in Central American, South African and Indian species, tannins and polyphenols in Indo-Chinese varieties and furanoid norditerpenes (diosbulbins) mostly in China. Diosbulbin D (0.07 mg/g) is a major toxic compound in Australian variety of *D. bulbifera*. Treatment practices varying from baking, followed by overnight leaching of the sliced tubers for 12 h in running water, resulted in reduction of major bitter and toxic compound to a very low level under the taste threshold rendering the final food palatable [86].

## Drug Interaction Study

*D. bulbifera* and Diosgenin effect on rat CYP450 enzymes and its important isoforms (CYP3A4, CYP2D6) was studied using high through put screening. In fluorometric assay, herb extract exhibited higher IC values (96.21 ± 1.32 to 180.42 ± 0.12 µg/ml) when compared to positive inhibitors and lower than Diosgenin (172.54 ± 0.52 to 201.86 ± 1.49 µg/ml) on CYP3A4 and CYP2D6. Based on the inhibitory potential, test substances exhibited very less interaction capacity, thereby leading to less significant herb-drug interaction with co-administered drugs [87]. Synergistic compatibility detoxification, that is, combining *D. bulbifera* with other herbal medicines, has been shown to improve therapeutic effects and reduce toxic effects. Combination with *Angelica sinensis* can enhance *D. bulbifera's* anti-tumor effect [88] and reduce renal toxicity [89-92] and kidney toxicity [93]. Combination with *Schisandra chinensis* relieved the liver damage caused by *D. bulbifera* [94-96]. Potential synergistic anticancer activity of combination of diosbulbin B with scutellarin from *Scutellaria barbata* proved useful for the clinical treatment of cancer [97]. Combination with *Glycyrrhiza uralensis* reduced liver damage and renal toxicity of *D. bulbifera* [98].

## Conclusion

*Dioscorea bulbifera* is one of the most widely-consumed aerial yam widely distributed throughout various tropical regions. The plants are characterized by the production of considerable number of aerial tubers or bulbils. *Dioscorea bulbifera* is widely used in traditional medicine among them many documented medicinal folk uses of the plant are presented here. It is reported to have wide chemical diversities as contains steroids, saponins, flavonoids, glycosides, tannins, alkaloid, fatty acids and essential oils. The plant appears to have a broad spectrum of activity on several ailments. Various parts of the plant have been explored for antitumor, anti HIV, antidyslipidemic, analgesic, anti-inflammatory, diuretic, gastroprotective, antioxidant, antimicrobial, antiviral, antifungal, anthelmintic, neuropharmacological, cardioprotective, anorexiant, plasmid curing activities and anti-hyperthyroid activities.

The pharmacological studies reported in the present review confirm the therapeutic value of *Dioscorea bulbifera*. Many polyherbal formulations containing this plant parts are available in the market. However, less information is available regarding the clinical study, standardisation method to avoid biological and geographical variation, advance food processing and detoxication techniques. The plant is pre-clinically evaluated to some extent; if these claims are scientifically and clinically evaluated then it can provide good remedies and help mankind in various ailments.

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