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Medicinal chemistry

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Phytochemistry and Therapeutic Potential of Medicinal Plant: *Dioscorea bulbifera*

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Abstract

Dioscorea bulbifera is an immensely important medicinal plant which is extensively used in both Indian and Chinese system of traditional medicine. It is found in many parts of the world and has gained wide attention not only for health care but also as a food crop. It has attracted scientific interest owing to its numerous therapeutic applications in various pathophysiological conditions like ulcers, sores, wound, spasms, dysentery, diabetes and cancer. Spectacular success in extensive research particularly within last two decades has proven that these activities are attributed to its unique phytochemistry. Bioactive components from *D. bulbifera* have exhibited anti-oxidant, anti-inflammatory, antibacterial, plasmid curing, antidiabetic and anticancer activities. It has become a model system in nanobiotechnology as it harbours phytochemicals with reducing, capping and shape modulating efficiencies. Numerous studies, either separately or in association, have aimed to explain the chemical composition and mechanisms behind its pharmacognostic significance. Similarly, many reports have documented and validated the claimed traditional usage by providing a strong scientific rationale. However, there is no review published on its *in vitro*, *in vivo* and *in silico* applications along with detailed phytochemistry. In view of the background, this review elaborates the complete phytochemistry of *D. bulbifera* with therapeutic importance.

Keywords: *Dioscorea bulbifera*; Phytochemistry; Traditional medicine; Diabetes; Cancer; Nanoparticles

Introduction

Medicinal plants are rich source of diverse phytochemicals with multifaceted therapeutic potential [1]. *Dioscorea bulbifera* is one of the unique medicinal plants among 600 species in the family Dioscoreaceae which has found its importance in traditional medicine throughout the world. Aglycons of its steroid saponins like diosgenin have gained attention as precursors in the synthesis of sex hormones, cardiatonic glucosides, fertility control compounds, corticosteroids and anabolic agents [2]. In Bangladesh it is used for treatment of leprosy and tumours while in Chinese medicine as a remedy for sore throat and for struma [3,4]. Similarly, it is applied on cuts and sores as infusion in Zimbabwe, while for treatment of abscesses, boils and wound infections in Cameroon and Madagascar [5]. It has got its wide applications in piles, ulcers, pain and inflammation in Indian traditional medicine [6,7]. Ancient and modern literature on its medicinal use have indicated that its tubers have therapeutic benefits as purgative, anthelmintic, diuretic, deflatulent, rejuvenating tonic, aphrodisiac and can also be used for treatment in scrofula, haematological disorders, diabetic disorders, worm infestations, haemorrhoids, skin disorders, general debility as well as polyurea (Figure 1). Crushed tubers and decoction are emulsified into oil to treat infected ulcers and sinus [8,9]. It is profusely used in both Indian and Chinese traditional medicine to cure gastric cancer and carcinoma of rectum and goitre [10]. Similarly, its extracts are reported to be antihyperlipidemic, antitumor, antioxidant, anorexiant, analgesic, anti- inflammatory, plasmid curing, antidiabetic and antihyperglycemic [11-17]. Dried yam is known to dissolve toxins, cures carbuncles, scrofula and purulent infections. It is considered as remedy against dysentery and diarrhoea in addition to syphilis in Java and Brazil. Interestingly, it is used against dog bites, snake bites and food poisoning in China, in addition to hepatic fibrosis by protecting the liver [18] It is also reported to have remedial potential against conjunctivitis, leucoderma, dyspepsia, urinary discharges, jaundice, diabetes, asthma, bronchitis, strangay and vata biliousness [19]. More recently, we have shown that its unique phytochemistry enables it to synthesize both gold (AuNPs) and silver nanoparticles (AgNPs) [20,21]. In the recent past, *D. bulbifera* has emerged as a promising complementary and alternative source of traditional medicine attracting prime attention towards spectacular scientific advancement in exploration of new biomolecules.

However, there are no reviews on *D. bulbifera* which elaborates its phytochemistry providing a strong scientific rationale supporting its immense applications in therapy. Hereby, scientific literature to address this lacuna bridging the gap between traditional use and modern scientific research on the complex medicinal chemistry of *D. bulbifera* is of utmost importance for future researches. In view of this background, herein we present the first detailed review on phytochemistry and therapeutic potential of *D. bulbifera* (Table 1).

Phytochemicals from *D. bulbifera*

The phytochemical diversity of *D. bulbifera* exhibits pronounce variation according to its geographical location, parts of plant and the solvent for extraction used. Flavonoids are effectively extracted in ethyl acetate soluble fraction of 75 % ethanol extract of the rhizomes of *Dioscorea bulbifera* from China which consist of both flavonol aglycones, namely kaempferol-3,5-dimethyl ether, caryatin, (+)-catechin and flavonol glycosides, namely, quercetin-3-*O*-galactopyranoside, myricetin-3-*O*-galactopyranoside, myricetin-3-*O*-glucopyranoside [12]. 8-epidiosbulbin E acetate (EEA) was isolated from aqueous methanolic extract of bulbs from India [16]. Diosbulbin B is a demethyl diterpenoid found as a main constituent of chloroform fraction (Figure 2) [22]. 80 % ethanolic extract was reported for efficient

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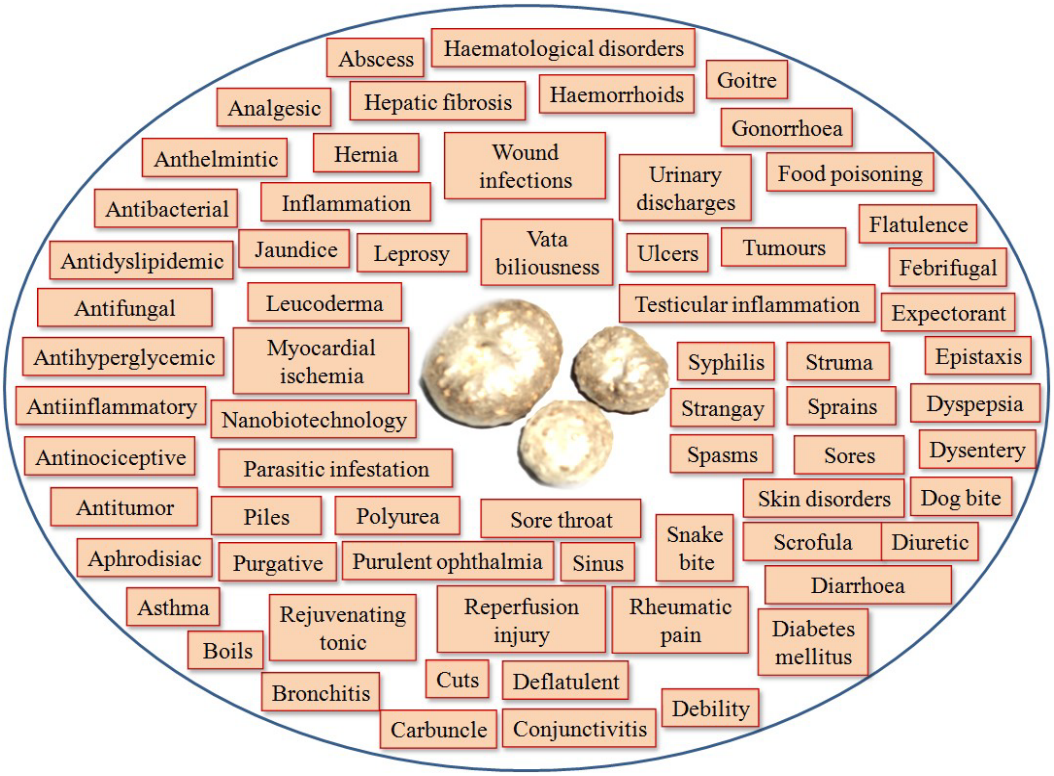


Figure 1: Therapeutic applications of *D. bulbifera*.

Sr. No.	Phytomemicals	Plant part	Country	Reference/s
1.	Diosbulbin A	Tuber, leaf, stem	China	[23,4]
2.	Diosbulbin B	Tuber, rhizome, Leaf, stem	China	[23,25,24, 22, 12, 4]
3.	Diosbulbin C	Tuber, leaf, stem	China	[23,4]
4.	Diosbulbin D	Tuber, leaf, stem	China, Bangladesh	[23,24,4,3]
5.	Diosbulbin E	Rhizome, leaf, stem	China	[25,4]
6.	Diosbulbin F	Tuber, rhizome, leaf, stem	China	[23,25,4]
7.	Diosbulbin G	Tuber, rhizome, leaf, stem	China	[23,25,4]
8.	Diosbulbin H	Leaf, stem	NI	[4]
9.	Diosbulbin I	Root tuber	China	[24]
10.	Diosbulbin J	Root tuber	China	[24]
11.	Diosbulbin K	Rhizome	China	[25]
12.	Diosbulbin L	Rhizome	China	[25]
13.	Diosbulbin M	Rhizome	China	[25]
14.	Diosbulbin N	Tuber	China	[23]
15.	Diosbulbin O	Tuber	China	[23]
16.	Diosbulbin P	Tuber	China	[23]
17.	Bafoudiosbulbin A	Bulbil, tuber	Cameroon	[28,29,30]
18.	Bafoudiosbulbin B	Bulbil, tuber	Cameroon	[28,29,30]
19.	Bafoudiosbulbin C	Bulbil, tuber	Cameroon	[28,30]
20.	Bafoudiosbulbin F	Bulbil	Cameroon	[28,30]
21.	Bafoudiosbulbin G	Bulbil	Cameroon	[28,30]
22.	Diosbulbisin A	Rhizome	China	[26]
23.	Diosbulbisin B	Rhizome	China	[26]
24.	Diosbulbisin C	Rhizome	China	[26]
25.	Diosbulbisin D	Rhizome	China	[26]
26.	Diosbulbiside A	Rhizome	China	[26]
27.	Diosbulbiside B	Rhizome	China	[26]
28.	Diosbulbiside C	Rhizome	China	[26]
29.	Dioscoreanoside A	Flower	Cameroon	[32]
30.	Dioscoreanoside B	Flower	Cameroon	[32]
31.	Dioscoreanoside C	Flower	Cameroon	[32]
32.	Dioscoreanoside D	Flower	Cameroon	[32]
33.	Dioscoreanoside E	Flower	Cameroon	[32]
34.	Dioscoreanoside F	Flower	Cameroon	[32]
35.	Dioscoreanoside G	Flower	Cameroon	[32]
36.	Dioscoreanoside H	Flower	Cameroon	[32]
37.	Dioscoreanoside I	Flower	Cameroon	[32]
38.	Dioscoreanoside J	Flower	Cameroon	[32]
39.	Dioscoreanoside K	Flower	Cameroon	[32]
40.	Daucosterol	Rhizome	China	[22]
41.	β-Sitosterol	Rhizome, tuber	China, Cameroon	[22,29]
42.	Palmatic acid	Rhizome	China	[22]
43.	Succinic acid	Rhizome	China	[22]
44.	Shikimic acid	Rhizome	China	[22]
45.	3, 5-dimethoxykaempferol	Rhizome	China	[22]
46.	3, 5, 3′-trimethoxyquercetin	Rhizome	China	[22]
47.	Caryatin	Rhizome	China	[22,12]
48.	(+)Catechin	Rhizome	China	[33,22,12]
49.	Myricetin,	Rhizome	China	[22,12,9]
50.	Myricetin-3-*O*-β-*D*-galactopyranoside,	Rhizome	China	[22]
51.	Myricetin-3-*O*-β-*D*-glucopyranoside	Rhizome	China	[22]
52.	Hyperoside	Rhizome	China	[22]

53.	Kaempferol	Rhizome, bulbil	China, Cameroon	[33,22,29]
54.	Kaempferol-3-*O*-β-*D*-galactopyranoside	Rhizome	China	[22]
55.	Kaempferol-3-*O*-β-*D*-glucopyranoside	Rhizome	China	[22]
56.	Protocatechuic acid	Rhizome	China	[34,22]
57.	Vanillic acid	Rhizome	China	[22,9]
58.	Isovanillic acid	Rhizome	China	[22,9]
59.	(+)Epicatechin	Rhizome	China	[22,9]
60.	Methyl-*O*-α-*D*-fructofuranoside	Rhizome	China	[22]
61.	Butyl-*O*-α-*D*-fructofuranoside	Rhizome	China	[22]
62.	Ethyl-*O*-β-*D*-fructopyranoside	Rhizome	China	[22]
63.	Butyl-*O*-β-*D*-fructopyranoside	Rhizome	China	[22]
64.	3-Phenyl-2-propenyl-*O*-β-*D*-glucopyranoside	Rhizome	China	[22]
65.	2-(4-methoxyphenyl)-ethyl-*O*-β-*D*-glucopyranoside	Rhizome	China	[22]
66.	Phenyl-methyl-*O*-β-*D*-glucopyranoside	Rhizome	China	[22]
67.	Kaempferol-3,5-dimethyl ether	Rhizome	China	[12]
68.	Quercetin-3-*O*-galactopyranoside	Tuber, Rhizome	Cameroon, China	[29,12]
69.	Myricetin-3-*O*-galactopyranoside	Rhizome	China	[12]
70.	Myricetin-3-*O*-glucopyranoside	Rhizome	China	[12]
71.	8-epidiosbulbin E acetate	Bulb, tuber	India, Bangladesh	[16,3]
72.	Demethyl batatasin IV	Tuber, bulbil	China, Nigeria	[24,31]
73.	Diosbulbinoside D	Leaves, stem	NI	[4]
74.	Diosbulbinoside F	Leaves, stem	NI	[4]
75.	Diosbulbinoside G	Rhizome	China	[25]
76.	C22 ω-hydroxy fatty acid	Tuber	China	[33]
77.	3-hydroxy-5-methoxybenzoic acid	Tuber	China	[33]
78.	Batatasin III	Tuber	China	[33]
79.	1,6-dihydroxy-2,5,7-trimethoxyphenanthrene	Tuber	China	[33]
80.	2,4,6,7-tetrahydroxy-9,10-dihydrophenanthrene	Tuber	China	[33]
81.	2,5,2',5'-tetrahydroxy-3'-methoxybibenzyl	Tuber	China	[33]
82.	Thunalbene	Tuber	China	[33]
83.	2,4-dimethoxyphenanthrene-3,7-diol	Tuber	China	[33]
84.	Flavanthrinin	Tuber	China	[33]
85.	Isorhamnetin	Tuber	China	[33]
86.	Quercetin	Tuber	China, Cameroon	[33,29]
87.	3,5,3'-trimethoxyquercetin	Tuber	China	[33]
88.	(-)-epicatechin	Tuber	China	[33]
89.	Isoquercitrin	Tuber	China	[33]
90.	2,7-dihydroxy-3,4,6-trimethoxyphenanthrene	Tuber	China	[33]
91.	Diarylheptanone	Tuber	China	[33]
92.	Pennogenin	Rhizome	China	[26]
93.	Pennogenin-3-*O*-α-L-rhamnopyranosyl-(1→3)-[α-L-rhamnopyranosyl-(1→2)]-*β*-D- glucopyranoside	Rhizome	China	[26]
94.	Pennogenin-3-*O*-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-*β*-D- glucopyranoside	Rhizome	China	[26]
95.	4-hydroxy-[2-trans-3',7'-dimethyl-octa-2',6'-dienyl]-6-methoxy acetophenone	Bulbs	India	[7]
96.	4,6-dihydroxy-2-O-(4'-hydroxybutyl) acetophenone	Bulb	India	[7]
97.	2,7-dihydroxy-4-methoxyphenanthrene	Bulbil, tuber	Cameroon	[28,29]
98.	3-O-α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→3)]-β-D-g1ucopyranosyl pennogenin (spiroconazol A)	Flower, tuber	Cameroon	[32,29,30]
99.	Quercetin-3-O-β-D-glucopyranoside	Tuber	Cameroon	[29]
100.	Diosgenin	Bulb, corm	India	[35,36]
101.	Smilagenone	Corm	India	[36]
102.	Epismilagenin	Corm	India	[36]
103.	Pennogenin 3-O-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside	Flower	Cameroon	[32]
104.	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	Flower	Cameroon	[32]
105.	23β,27-dihydroxy-pennogenin 3-O-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside	Flower	Cameroon	[32]
106.	Floribundasaponin B	Flower	Cameroon	[32]
107.	Stigmasterol	Tuber	China	[24]
108.	Lutein	Tuber	India	[27]
109.	Neoxanthin	Tuber	India	[27]
110.	Violaxanthin	Tuber	India	[27]
111.	Zeaxanthin	Tuber	India	[27]
112.	Auroxanthin	Tuber	India	[27]
113.	Cryptoxanthin	Tuber	India	[27]
114.	Tetracosanoic acid,	Tuber	Cameroon	[29]
115.	1-(tetracosanoyl)-glycerol	Tuber	Cameroon	[29]
116.	trans-tetracosanylferulate	Tuber	Cameroon	[29]

117.	3-O-β-D-glucopyranosyl-b-sitosterol	Tuber	Cameroon	[29]
118.	3,5,4'-trihydroxy-3'-methoxybibenzyl	Bulbil	Cameroon	[29]
119.	Sinodiosgenin	Corm	India	[36]
120.	Dioscin	Rhigoma	China	[25]
121.	Mono-arachidin	Tuber	China	[34]
122.	1,7-bis-(4-hydroxyphenyl)-1E,4E,6E-heptatrien-3-one	Tuber	China	[34]
123.	Behenic acid	Tuber	China	[34]
124.	2,3'-di-hydroxy-4',5'-dimethoxybibenzyl	Tuber	China	[34]
125.	Docosyl ferulate	Tuber	China	[34]
126.	7-bis-(4-hydroxyphenyl) -4E, 6E-	Tuber	China	[34]
heptadien-3-one				
127.	5,3,4-trihydroxy-3,7-dimethoxyflavone	Tuber	China	[34]
128.	Tristin	Tuber	China	[34]

NI = No information available in the literature.

Table 1: Phytochemicals isolated from *D. bulbifera*.

extraction of epicatechin, isovanillic acid, vanillic acid and myricetin [9]. Similarly, *D. bulbifera* from China contains diosbulbin A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P as major phytochemicals [4,23-25]. Steroidal sapogenins named diosbulbisins A, B, C, D, spirostane glycosides named diosbulbisides A, B and cholestane glycoside named diosbulbiside C were found to be predominant in 95 % ethanolic extract of rhizomes of China (Figure 3) [26] Carotenoids such as lutein, zeaxanthin, neoxanthins are also prevalent in *D. bulbifera* [27]. Methanolic extract of bulbils from Cameroon are found to be rich in clerodane diterpenoids, bafoudiosbulbins A, B, C, F and G (Figure 4) [28-30]. Phytoalexin called demethylbatatasin IV and norditerpenoid diosbulbin D were isolated from bulbils from Nigeria and tubers from Bangladesh, respectively (Figures 5 and 6) [3,31]. Flowers of *D. bulbifera* from Cameroon has wide range of steroidal saponins namely, dioscoreanosides A, B, C, D, E, F, G, H, I, J and K (Figure 7) [32].

Medicinal Use

Goitre

Tubers of *D. bulbifera* are steeped in white wine for a week which is traditionally recommended as infused wine and taken daily to get benefits in treatment of goitre. Formulations have profound applications as clinical medicine to treat thyroid glands [9,18,25].

Respiratory disorders

Fresh tuber pieces are pounded with black pepper followed by mixing with curd is taken against cough and cold in India. Similarly, roasted, peeled and dried powder is known to cure respiratory problems when taken with honey. Bitter bulbils are useful against severe cough while edible normal tubers are used against asthmatic conditions. In China, it is considered as a styptic against lung bleeding and epistaxis [18].

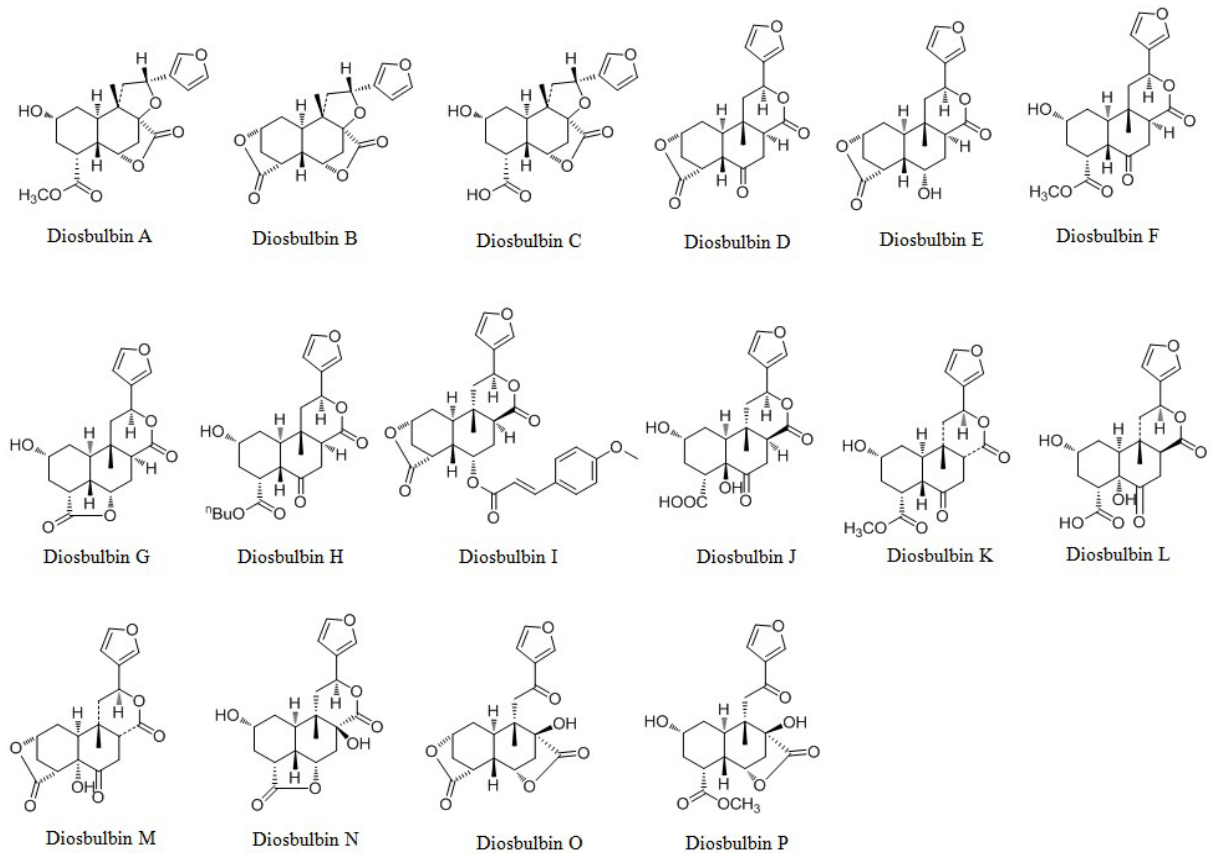


Figure 2: Norclerodane diterpenoids isolated from *D. bulbifera*.

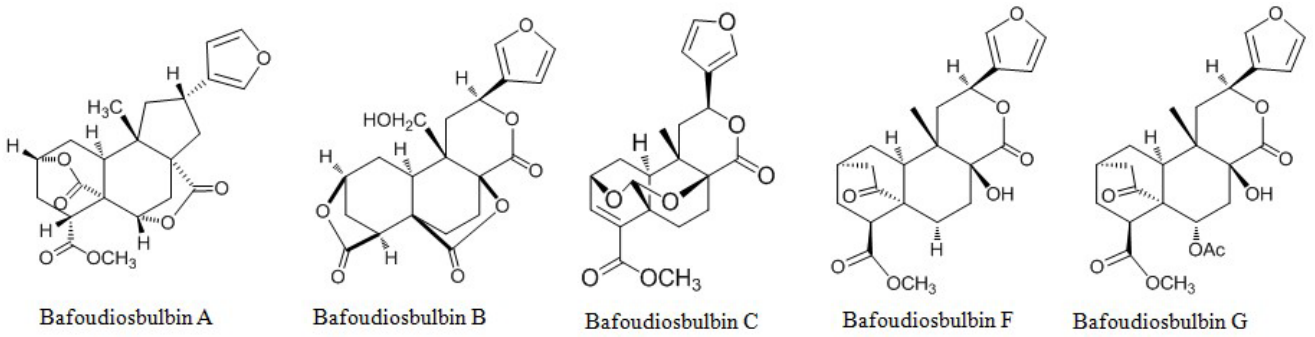


Figure 3: Clerodane diterpenoids isolated from *D. bulbifera*.

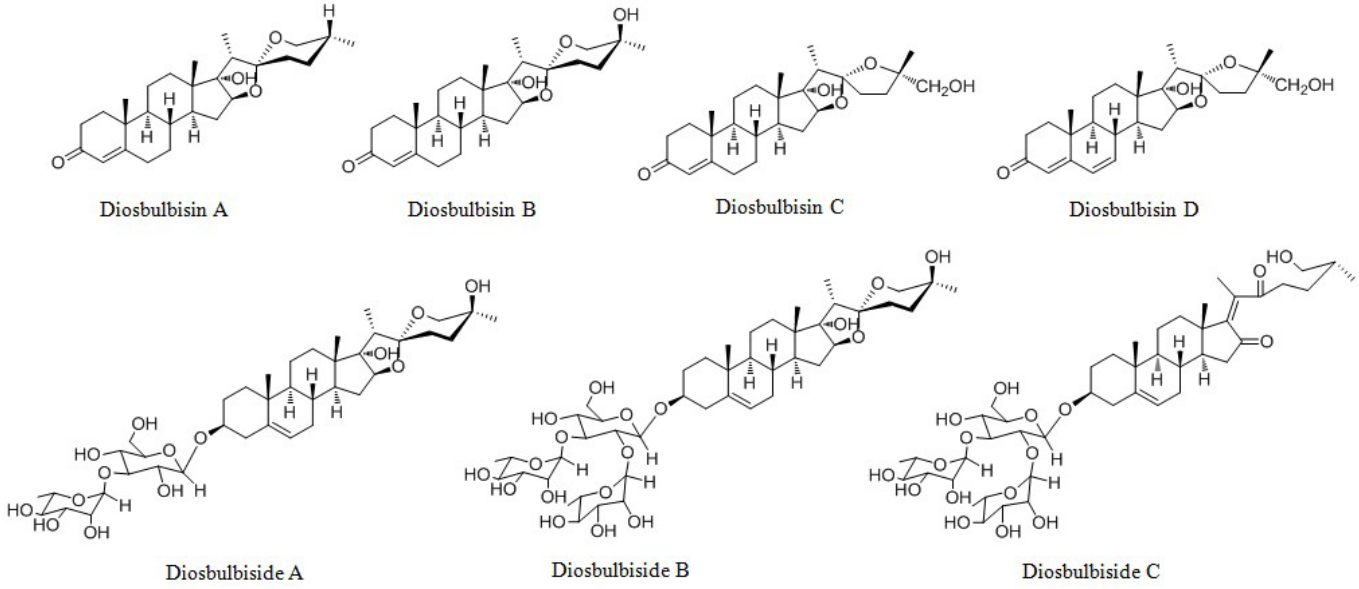


Figure 4: Steroidal sapogenins, spirostane glycosides and cholestane glycosides isolated from *D. bulbifera*.

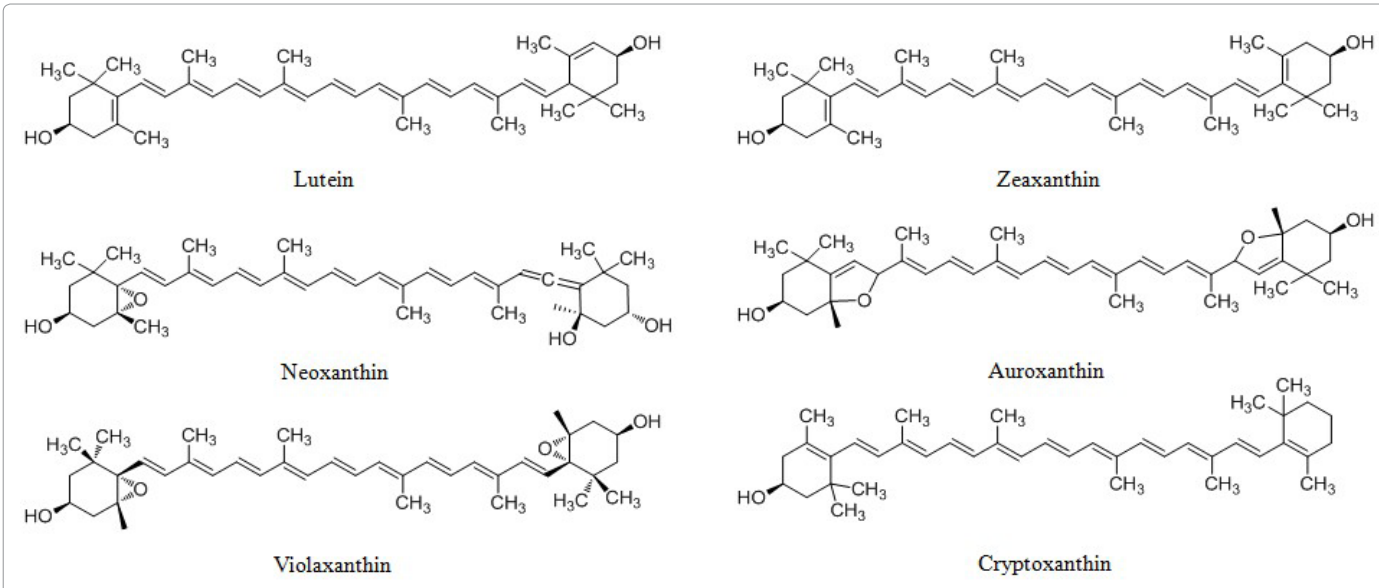


Figure 5: Carotenoids isolated from *D. bulbifera*.

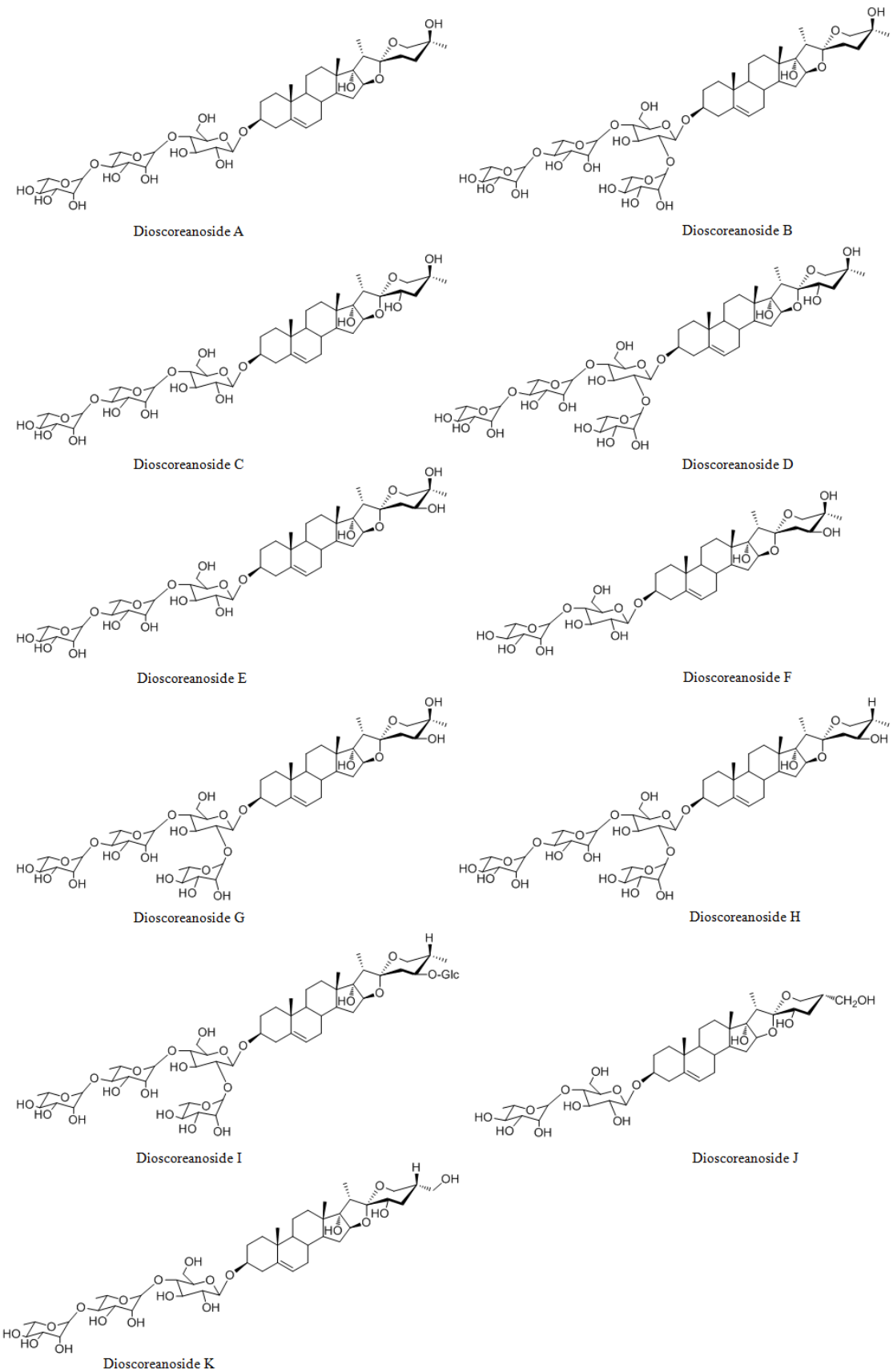
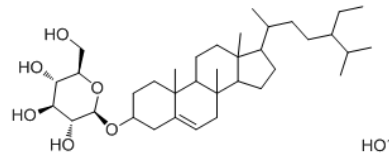
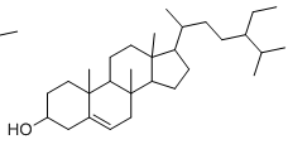
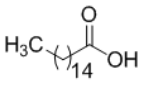
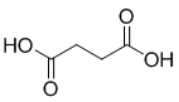


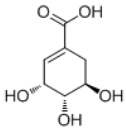
Figure 6: Steroidal saponins of dioscoreanosides series isolated from *D. bulbifera*.

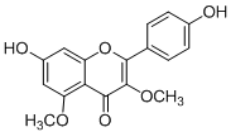

Daucosterol

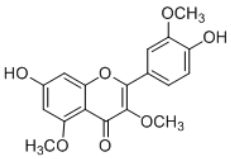

β-Sitosterol

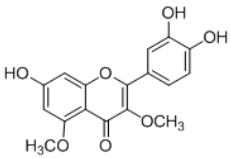

Palmitic acid

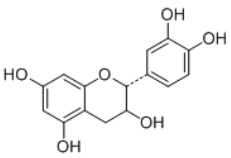

Succinic acid

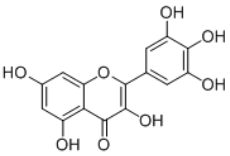

Shikimic acid

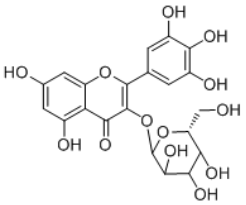

3, 5 – dimethoxy kaempferol

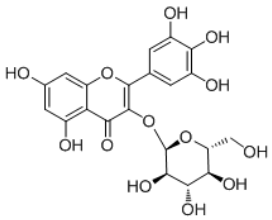

3, 5, 3′-trimethoxy quercetin


Caryatin


(+) Catechin


Myricetin


Myricetin-3-*O*-β-*D*-galactopyranoside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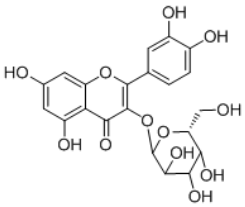
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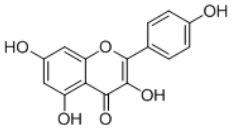
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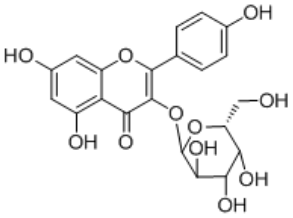
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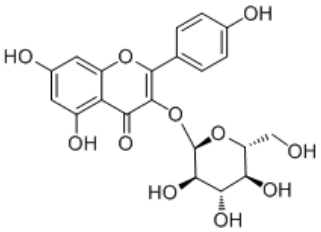
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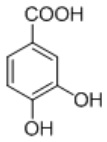
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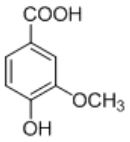
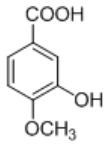
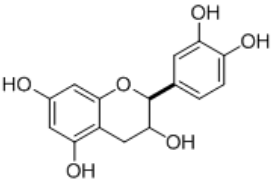

Vanillic acid


Isovanillic acid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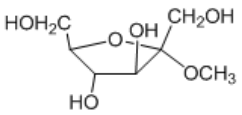
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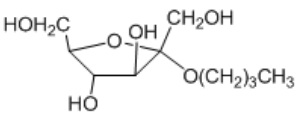
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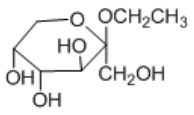
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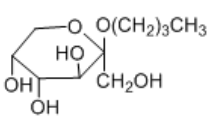
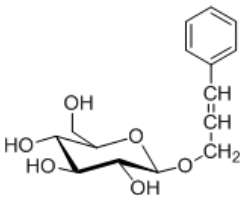

Butyl-*O*-β-*D*-fructopyranoside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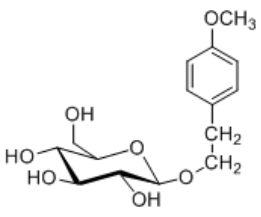
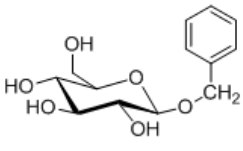

2-(4-methoxyphenyl)-ethyl-*O*-β-*D*-glucopyranoside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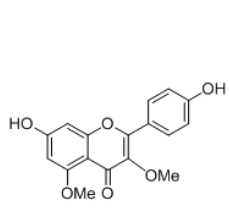
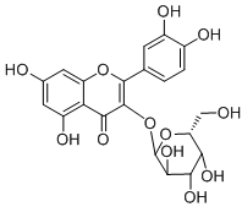


Kaempferol-3,5-dimethyl ether



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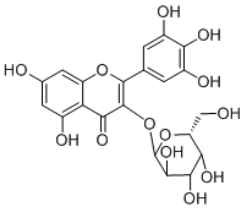

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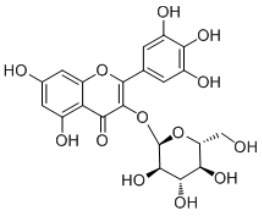

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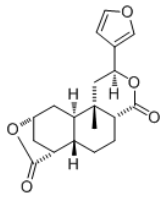
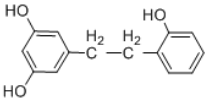
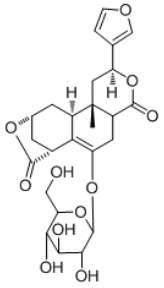


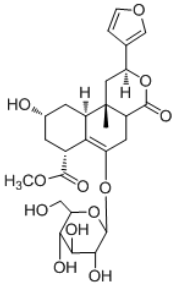
8-epidiosbulbin E acetate



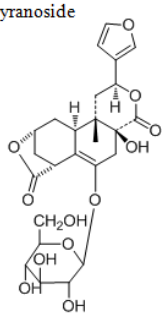
Demethyl batatasin IV



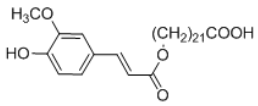
Diosbulbinoside D



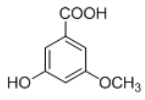
Diosbulbinoside F



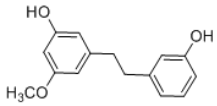
Diosbulbinoside G



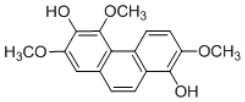
C_{22} ω-hydroxy fatty acid



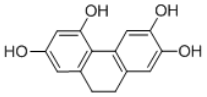
3-hydroxy-5-methoxybenzoic acid



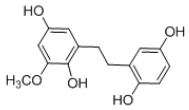
Batatasin III



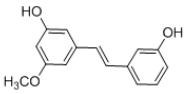
1,6-dihydroxy-2,5,7-trimethoxyphenanthrene



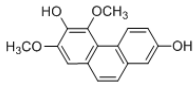
2,4,6,7-tetrahydroxy-9,10-dihydrophenanthrene



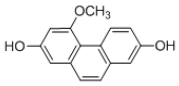
2,5,2',5'-tetrahydroxy-3'-methoxybibenzyl



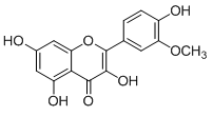
Thunalbene



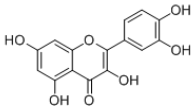
2,4-dimethoxyphenanthrene-3,7-diol



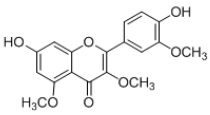
Flavanthrinin



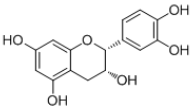
Isorhamnetin



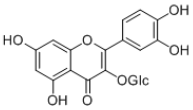
Quercetin



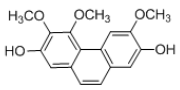
3,5,3'-trimethoxyquercetin



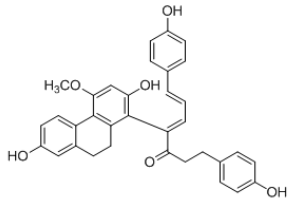
(-)-epicatechin



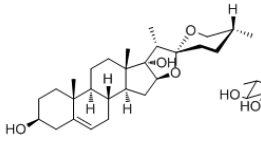
Isoquercitrin



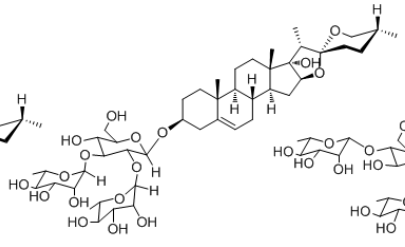
2,7-dihydroxy-3,4,6-trimethoxyphenanthrene



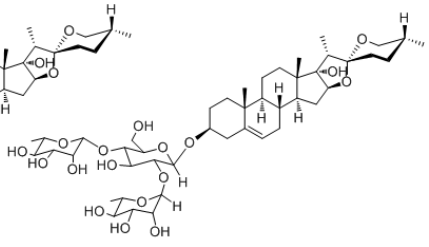
Diarylheptanone



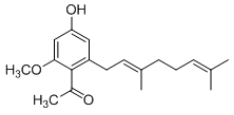
Pennogenin



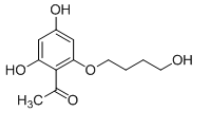
Pennogenin-3-*O*-α-L-rhamnopyranosyl-(1→3)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside



Pennogenin-3-*O*-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside



4-hydroxy-[2-trans-3',7'-dimethyl-octa-2',6'-dienyl]-6-methoxy acetophenone



4,6-dihydroxy-2-O-(4'-hydroxybutyl) acetophenone

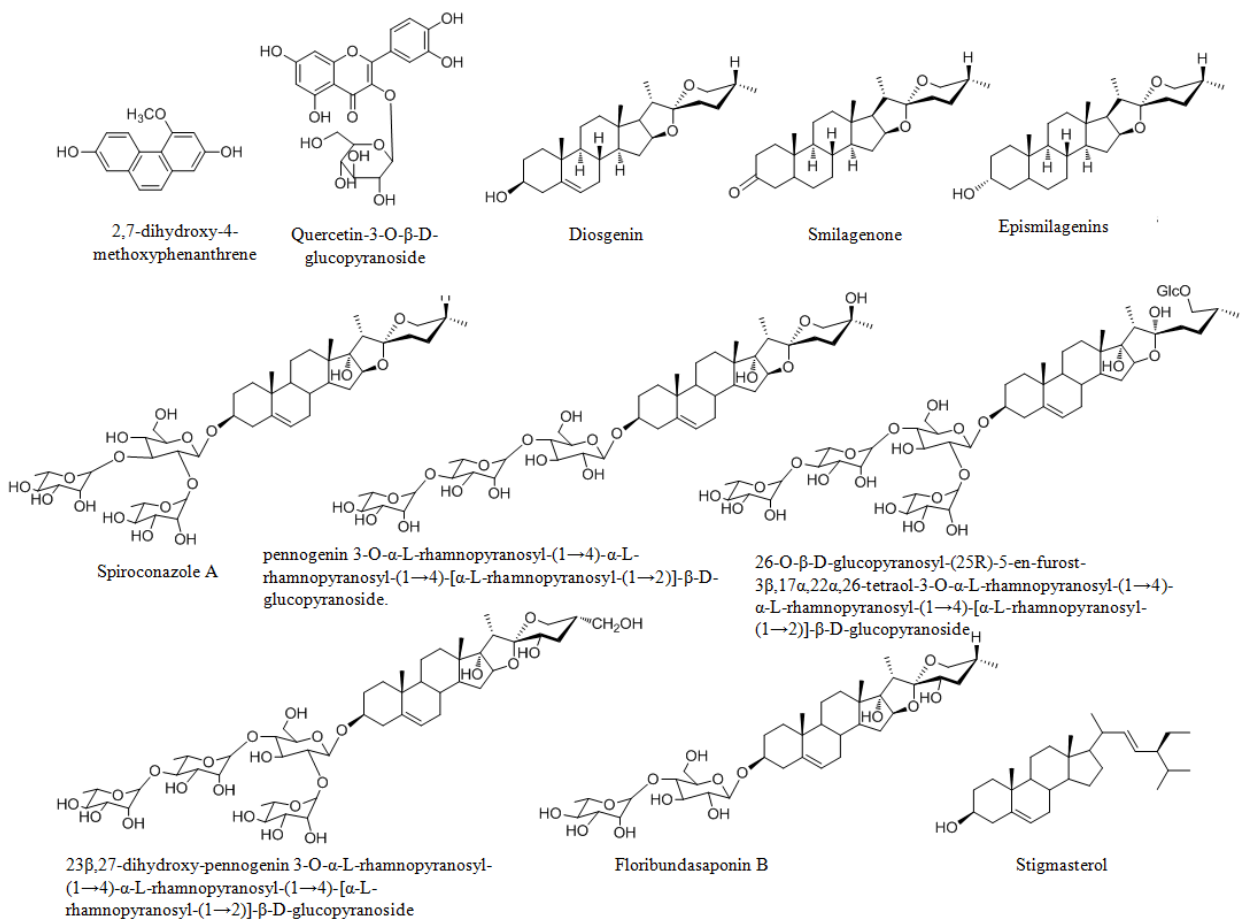


Figure 7: Diversified phytochemistry of *D. bulbifera*.

Eye disorder

D. bulbifera serves as a well-known ophthalmic remedy. Purulent ophthalmia is treated with sap from stem as eye drops in Congo. Wakefulness is promoted in Ivory Coast by stillation of leaf sap into the eye. A potion made out of steamed leaf is used in east Africa for treating a type of conjunctivitis called „pink eye"[18].

Parasitic infections

D. bulbifera from Southwest Nigeria is reported to show anthelmintic activity as one of its significant ethnobotanical application when eaten after roasting. Scientific evidence to the fact was provided by a recent study confirming *in vitro* anthelmintic activity of methanol extracts of the flesh and peel of *D. bulbifera* bulbils. The extracts rich in phenolics (tannins, flavonoids), saponins as well as other secondary metabolites could efficiently show anthelmintic activity against *Pheritima posthuma* and *Fasciola gigantic*. Earthworms were paralysed in 5.6 min and death was observed in 10 min when treated with peel extract, while treatment with flesh extract showed paralysis in 8.4 min and death in 13.8 min at 100 mg/ml. Likewise, liverflukes were paralyzed after 10.2 min and died after 15.81 min at a concentration of 100 mg/ml of peel extract. The probable mechanism was explained to be the binding of phenolic and tannin compounds to glycoprotein present on the cuticle together with saponin mediated alteration of permeability and pore formation in the membrane of the parasite leading to paralysis and death [10].

Bacterial and fungal infections

D. bulbifera is known to be used for treatment of sexually transmitted diseases like gonorrhoea and syphilis in addition to sore throat in Chinese medicine. In Congo it is used against parasitic and fungal infections [18]. Its aqueous extract showed superior activity against *Escherichia coli* while ethanol extract was found to be potent against *Staphylococcus aureus* and *Candida albicans* [37]. Bacterial pathogens have posed a threat to the human health by developing multidrug resistance leading to re-emergence of diseases once controlled. Genetic determinants conferring resistance to one or more antibiotics are mostly located on plasmids which being extra chromosomal DNA, can be effectively transferred to other bacteria, co-existing in the same environment. This underlying mechanism for spread of antimicrobial resistance is an acute difficulty for treating infectious diseases which has led to the search of new drugs called plasmid-curing agents, although many of which such as acridine orange, ethidium bromide and sodium dodecyl sulphate, are toxic, mutagenic and carcinogenic. Hence, plasmid curing agents isolated from medicinal plants have gained more importance and are being investigated owing to their biocompatibility and minimum toxicity. Recently, norditerpene compound, 8-epidiosbulbin E acetate from *D. bulbifera* bulbs has exhibited significant broad spectrum potential to cure antibiotic resistance plasmids (R- plasmids) from clinical isolates although it showed low antimicrobial activity (MIC > 400 µg/mL) for all tested pathogens except *Escherichia coli* (pUC18) which showed an MIC = 200 µg/mL.

However, R-plasmids in clinical strains of *Enterococcus faecalis*, *E. coli*, *Shigella sonnei*, *Pseudomonas aeruginosa* and *Bacillus subtilis* were effectively cured. Plasmid curing by 8-epidiosbulbin E acetate resulted in effective reversal of bacterial resistance to multiple antibiotics in an *E. coli* strain that was resistant to gentamicin, kanamycin, neomycin, streptomycin, tetracycline, novobiocin, ciprofloxacin, cefoperazone, oxacillin, ceftazidin, co-trimazine, imipenem, cefalexin, cefotaxime, oxytetracycline, cloxacillin, doxycycline, levofloxacin, ofloxacin, gatifloxacin, moxifloxacin, norfloxacin, cefpirome and cotrimoxazole. Further, *S. sonnei* was sensitised to ampicillin, gentamicin, tetracycline, novobiocin, ciprofloxacin, cefoperazone, ceftazidime, oxacillin, ceftazidin, co - trimazine, imipenem, cefazolin, cefalexin, cefotaxime, levofloxacin, ofloxacin, norfloxacin, and cefpirome as a result of 8-epidiosbulbin E acetate mediated plasmid curing. Vancomycin-resistant *Enterococcus faecalis*, resistant to roxithromycin, cloxacillin, cefalexin and clindamycin became sensitive to these antibiotics after plasmid curing by 8-epidiosbulbin E acetate. Similarly, reference R-plasmids such as RP4, RMS163, RIP64 and pUB110 were also cured by 8-epidiosbulbin E acetate at curing efficiencies of 44%, 30%, 64% and 48%, respectively. Reduction of minimal inhibitory concentration (MIC) of antibiotics against MDR bacteria on curing of R-plasmid by 8-epidiosbulbin E acetate provided strong evidence for the novel mechanism behind the effective antibacterial treatment by *D. bulbifera* [16]. Additionally, vanillic acid and isovanillic acid have shown antibacterial activity [9]. In the western highlands of Cameroon, tubers of *D. bulbifera* are used against typhoid fever caused by *Salmonella typhi* and paratyphoid fever caused by *Salmonella paratyphi* A and *Salmonella paratyphi* B. Two clerodane diterpenoids, bafoudiosbulbins A and B were reported to have anti-bacterial activity when tested against *Salmonella typhi*, *Salmonella paratyphi* A, *Salmonella paratyphi* B, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* by using both agar diffusion and broth dilution techniques. Both bafoudiosbulbins A and B exhibited bactericidal activity selectively against *S. typhi*, *S. paratyphi* A and *S. paratyphi* B [29]. Isolated bafoudiosbulbins B, C, F and G, as well as crude ethyl acetate (EtOAc) extract (DBB1) and fractionated DBB2 obtained from methanolic extract of bulbils from *D. bulbifera* L. var sativa from Bafou village near Dschang (West region of Cameroon), showed growth inhibition in fifteen test strains (both clinical MDR and ATCC) of bacterial pathogens, namely, *E. coli*, *E. aerogenes*, *K. pneumoniae*, *P. aeruginosa*, *M. smegmatis* and *M. tuberculosis*. Selective inhibition of ATCC strain of *E. coli*, *E. aerogenes*, *K. pneumoniae*, *M. smegmatis* and *M. tuberculosis* as well as *E. coli* AG100A and *M. tuberculosis* MTCS2 by crude extracts can be considered as significant. Bafoudiosbulbin C was found to be active against *M. smegmatis* and *M. tuberculosis* ATCC and MTCS2 strains at a value as low as 8 µg/mL. Inhibitory effect of the compounds isolated from *D. bulbifera* against MDR bacteria such as *E. aerogenes* EA289, CM64, *K. pneumoniae* KP63 and *P. aeruginosa* PA124 was better than that of standard antibiotic chloramphenicol in absence as well as in presence of efflux pump inhibitor, phenylalanine arginine β- naphthylamide [28].

Inflammation and pain

D. bulbifera is used to treat inflammation associated dispersal of "lumps", hernia, sprain, injury, testicular inflammations, in China. Rheumatic pain and breast problems are relieved in Congo and Gabon, respectively by an ointment prepared by incorporation of bulbils into palm oil [18] It is also used as analgesic and antispasmodic. Vanillic acid and isovanillic acid present in *D. bulbifera* are reported to exhibit anti-inflammatory activity [9]. Recent *in vivo* studies of aqueous and methanol extracts from bulbils of *D. bulbifera* var sativa confirmed potent antinociceptive effect. A dose dependent reduction in the acetic acid induced abdominal constriction was observed in white adult mice *Mus musculus* (weighing 25–30 g), on oral administration of aqueous and methanol extracts. Similarly, in case of formalin- induced paw licking test, intraplantar injection of formalin (2.5%) into the right hind paw of adult Wistar rats (weighing 180–200 g), generated a classical biphasic nociceptive response that was significantly inhibited by aqueous and methanol extracts as compared to indomethacin. These extracts also presented important anti-inflammatory effects on pressure induced pain sensitivity, acute oedema induced by carrageenan, histamine, serotonin, formalin and chronic oedema induced by formalin [5]. Pronounced hypernociception induced by intraplantar injection of complete Freud's adjuvant (CFA) in Swiss mice, could be countered significantly (61 % inhibition) owing to the antinociceptive effect of methanol extract of *D. bulbifera* (MEDB) administered orally. Hypersensitivity in mice due to neuropathic pain induced by partial ligation sciatic nerve (PLSN) was significantly reduced (38 %) followed to oral administration of MEDB. Similarly, the extract even reduced LPS and PGE2 induced mechanical hypernociception and further study helped in partial prediction that the antinociceptive activities of *D. bulbifera* both in inflammatory and neuropathic models of pain were attributed to its ability to activate the NO–cGMP–ATP- sensitive potassium channels pathway [15].

Diabetes and digestive problems

Traditional use of *D. bulbifera* is known to lower glycemic index in Diabetes mellitus. Diosgenin has shown to ameliorate diabetic neuropathy [18]. A study carried out to evaluate aqueous extract of D. *bulbifera* tubers (DBEA003) for antihyperglycemic activity on streptozotocin (STZ) treated Wistar rats, provided scientific rationale behind the traditional use. A higher dose (1000 mg/kg p.o.) resulted in highly significant antihyperglycemic effect in glucose tolerance test bringing down the blood glucose level from 129±8.81 mg/dL (30 min) to 97±5.83 mg/dL (90 min). Remarkably, a long lasting glycemic control in diabetic condition was observed over administration of DBEA003, which might be attributed due to its action at the tissue or receptor level [17]. However, the actual mechanism of action by which *D. bulbifera* exerts the antidiabetic effect was furnished in our previous report where we confirmed the inhibition of two key enzymes, α-amylase and α-glucosidase. Petroleum ether, ethyl acetate and methanol extracts of *D. bulbifera* bulbs were obtained by sequential hot Soxhlet extraction among which ethyl acetate extract showed most superior activity of 73.39 % against porcine pancreatic α-amylase. Strongest inhibition against α-glucosidase was found for ethyl acetate extract (99.6 %) of *D. bulbifera* bulb [38]. Similarly, even among cold 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. The bioactive principle was identified as diosgenin which in its isolated form showed superior α-amylase and α-glucosidase inhibition upto 70.94 ± 1.24% and 81.71 ± 3.39%, respectively. The mechanism was established to be uncompetitive mode of binding to α-amylase as confirmed by decrease in both Km and Vm values. Further, hydrogen bonding between carboxyl group of Asp300 and hydrophobic interactions between Tyr62, Trp58, Trp59, Val163, His305 and Gln63 residues of α-amylase was indicated by molecular docking. Similarly, two catalytic residues (Asp352 and Glu411) from α-glucosidase were found to be the target of interaction with diosgenin [35]. Inhibition of digestive enzymes like α-amylase (132 ± 2%) and trypsin (4.3 ± 0.2 %) were also reported by crude extract of *D. bulbifera* tubers collected from the central region (Narayani Zone) of Nepal which were found to be rich in oxalate (67 ± 9 mg/100g), phytate (184 ± 14 mg/100g) and cyanogens (3.3 ± 0.9 mg HCN/Kg FW) [13].

Oxidative stress and degenerative diseases

Free radicals are key mediators for emergence of disease, progression and its associated pathology including diabetes, cancer and even AIDS [39]. Antioxidants, namely, epicatechin, isovanillic acid, vanillic acid, myricetin are important bioactive principles in *D. bulbifera* that are responsible for protection against cardiovascular diseases and styptic activities [9]. Tubers of *D. bulbifera* collected from Nepal showing superior DPPH radical scavenging, ferrous ion chelating, reducing power, and total antioxidant activity contained high oxalic acid (67 ± 9 mg/100g), citric acid (282 ± 24 mg/100g), malic acid(266 ± 20 mg/100g), succinic acid(2510 ± 108 mg/100g) and olyphenols (166 ± 10 mg/100g). Thus the chemical constituents might be playing the key role behind its pronounced antioxidant activity [13]. *D. bulbifera* from Guangzhou of China showed the highest phenolic content (59.43 mg GAE/g), that further exhibited most superior antioxidant property in terms of $ABTS^{+}$ radical scavenging activity (708.73 µmol Trolox/g) as well as ferric reducing antioxidant power (FRAP) assay (856.92 µmol Fe^{2+}/g) [40]. Ethyl acetate fraction of hydro alcoholic extract of *D. bulbifera* from China, yielded a bibezyl compound, 2,5,2',5'-tetrahydroxy-3'-methoxybibenzyl and diobulbinone A amongst which Trolox-equivalent antioxidant capacity of the new bibenzyl 7 was found to be 0.52 ± 0.01 by FRAP at a concentration of 1 mM. Similarly it showed an EC50 value of 2.57 ± 0.06 mM for DPPH radical scavenging. However, the new diarylheptanone, diobulbinone A did not show significant antioxidant activity at the same concentration by either of the methods [33]. Dried bulbs of *D. bulbifera* from India were reduced to fine powder and extracted with 70% (v/v) ethanol in distilled water which was further sequentially extracted with petroleum ether, ethyl acetate and methanol. Among the extracts, methanolic extract with maximum phenolic content (145.44 ± 3.29 µg/mL) showed most superior antioxidant activity proved to be a function of phenolic content. Percentage scavenging activity of methanolic extract against DPPH, hydroxyl, superoxide anion radical and nitric oxide was found to be 84.94 ± 0.62 %, 76.11 ± 1.26 %, 59.75 ± 0.98 % and 57.59 ± 0.64 %, respectively. Simultaneously, it scavenged pulse radiolysis generated $ABTS^{+}$ radical with a second order rate constant of 1.72×10^{6}, respectively. Similarly, ethyl acetate extract also showed higher percent scavenging activity of free radicals owing to its high phenolic content (98 ± 1.17 µg/mL) and 94.05 % diosgenin [41]. *D. bulbifera* (DB) tubers obtained from Mumbai, India, were extracted using a Soxhlet-extractor by 70% ethanol. Sprague– Dawley male rats were administered with 1 ml of DB extract dissolved in water (150 mg kg^{-1} of body weight) for 30 days, which resulted in significantly improved performance towards aortic flow (AF), left ventricular developed pressure (LVDP) and the first derivative of developed pressure (LVmax dp/dt) in DB treated hearts during post ischemic reperfusion. Additionally, marked reduction in myocardial infarct size (20 ± 2.64%) was observed in the treated group. Significant reduction of apoptotic cardiomyocytes (16.89 ± 1.7%) confirmed its anti-apoptotic activity. Increased Bcl2 expression and decreased Bax expression leading to reduction in Bax/Bcl2 ratio was evidenced. Further, upregulation of procaspase 3 and downregulation of cleaved caspase 3 coupled with prevention of loss of phase II enzyme HO-1 with proven cardioprotective ability considerably, provided a strong scientific rationale that *D. bulbifera* has the potential to ameliorate myocardial ischemia and reperfusion injury by improving ventricular function and inhibition of necrosis and apoptosis in cardiomyocytes [42].

Tumor and cancer

Aborigines from Tully district in North Queensland use a decoction of *D. bulbifera* against skin cancer [18]. Similarly it is also used in traditional Chinese medicine against cancer [25]. Phytochemicals present in extracts (75 % ethanol, v/v) of chipped rhizomes exhibited potent antitumor promoting properties. Among the flavonols, kaempferol-3,5-dimethyl ether (IC_{50}= 0.64 µg/mL) exhibited strongest inhibition followed by caryatin (IC_{50} = 3.0 µg/mL), myricetin (IC_{50} = 3.7 µg/mL) and (+)-catechin (IC_{50} = 13.1 µg/mL) against tumor promotion in JB6 (Cl 22 and Cl 41) cells induced by a promoter, 12-*O*-tetradecanoylphorbol-13-acetate (TPA). In contrast to aglycones, flavonol glycosides, quercetin-3-*O*-galactopyranoside, myricetin-3-*O*-galactopyranoside, myricetin-3-*O*-glucopyranoside showed a considerably reduced activity due to the presence of sugar moieties [12]. However, diosbulbin B with demethyl diterpenoid skeleton, selectively inhibited solid sarcoma 180 tumor growth in mice significantly, compared to A375-S2, Hela, L929 and JB6 cells as reported in various studies [12,22]. The study was conducted by administration of diosbulbin A (0.2 mg/head/day), diosbulbin B (0.2 mg/head/day) and diosbulbin A 2-O-β-D-glucopyranoside (0.2 and 0.1 mg/head/day) by i.p. daily for 5 days to male ddy mice inoculated with total of 180 sarcoma cells. Sixteen days after inoculation, the tumors were removed and weighed which revealed that diosbulbin B resulted in reduction of tumor weight by 57.89 % while diosbulbin A reduced upto 50.19 % [4] Further studies revealed moderate inhibitory effect of ethyl-*O*-β-D- fructo-pyranoside (IC50 > 30 µg/mL) and butyl-*O*-β-D-fructopyranoside (IC_{50} > 30 µg/mL) from *D. bulbifera* on JB6 neoplastic transformation [22]. In another study, norditerpene compound, 8-epidiosbulbin E acetate failed to show any cytotoxicity against variety of human cancer cells, namely MCF-7 (breast cancer), SiHa (cervical cancer) and A431 (epidermal carcinoma), ensuring its potential to be used in non-cancer drug discovery programmes [16]. Dried rhizomes of *D. bulbifera,* collected from Anhui Province of China containing pennogenin-3-*O*-α-L-rhamnopyranosyl-(1→3)-[α-L-rhamnopyranosyl-(1→2)]-*β*- D-glucopyranoside and pennogenin-3-*O*-α-L-rhamnopyranosyl-(1→4)-[α-L- rhamnopyranosyl-(1→2)]-*β*-D-glucopyranoside showed 99.1% and 92.6% inhibition against human hepatocellular carcinoma cells and Bel7402, respectively at a concentration of 10 µM. The compounds further, exhibited cell growth inhibition toward SMMC7721 human hepatocellular carcinoma cells [26]. Diosbulbins N, O, P showed lower activity (IC_{50} > 40µM) when tested against five cancer cell lines, namely, HL-60, SMMC7721, A549, MCF7 and SW480 for their cytotoxic activity [23]. Cytotoxicity studies on ECV304 cells (urinary bladder carcinoma cells), revealed that the isolated spirostanol derivatives, pennogenin 3-O-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (IC50 = 8.5 µg/mL) and spiroconazol A (IC_{50} = 5.8 µg/mL) showed moderate inhibition due to membrane toxicity via LDH liberation. However, the furostanol derivative, 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 (IC_{50} = 14.3 µg/mL), also showed a moderate activity, but by a direct influence of the mitochondrial metabolism, without liberation of LDH [32].

Synthesis of Nanoparticles

In spite of having a treasure of diverse groups of phytochemicals, *D. bulbifera* was not explored in the field of nanobiotechnology, until recently. We had reported for the first time the potential of its tuber extract to synthesize AuNPs of exotic shapes, namely gold nanotriangles, nanoprisms, nanotrapezoid and spheres in a range from 50 to 300 nm. Maximum synthesis of AuNPs was achieved at 50°C by complete reduction of 1 mM chloroauric acid at 90 mins which was found to be faster as compared to maximum synthesis of AuNPs after 5 h by *Plumbago zeylanica* root extract (PZRE) [20,43]. Rapid

reduction by *D. bulbifera* tuber extract (DBTE) might be due to its high total reducing sugar content (3.41± 0.15 mg/mL) and high flavonoid content (4 ± 0.12 mg/mL) while PZRE contained 1.25 ±0.04 mg/mL and 0.95 ± 0.05 mg/mL of total reducing sugar and total flavonoids, respectively. Further, the aqueous tuber extract synthesized anisotropic AgNPs in the form of rare nanotriangles, nanorods, spheres and hexagons in the size range of 8–20 nm at 50°C with 0.7 mM $AgNO_3$ solution in 5 h. Bioreduced AgNPs possessed potent antibacterial activity against both Gram-negative bacteria, namely *Acinetobacter baumannii, Enterobacter cloacae, Escherichia coli, Haemophilus influenza, Klebsiella pneumonia Neisseria mucosa, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, Serratia odorifera, Vibrio parahaemolyticus* and Gram-positive bacteria, namely, *Bacillus subtilis, Paenibacillus koreensis* and *Staphylococcus aureus.* A selective synergistic activity was observed where β- lactam, piperacillin exhibited 3.6 fold increase while macrolide, erythromycin showed 3 fold increase in potency against multidrug-resistant *A.baumannii* when combined with AgNPs. Likewise, a combination of AgNPs with chloramphenicol and vancomycin against *P. aeruginosa* resulted in 4.9-fold and 4.2-fold increase in zone diameter, respectively. 11.8-fold increase in zone diameter of streptomycin in combination with AgNPs against *E. coli* was found to be most significant. The unique phytochemistry of *D. bulbifera* with both reducing agents like ascorbic acid, citric acid and phenolics along with starch as capping agent and saponins helped in reduction, stabilization and shape evolution of nanoparticles [21].

Toxicity and Detoxification

Roots of *D. bulbifera* from China are reported as toxic, thereby might have achieved limited focus on its use in traditional medicine. Dioscin and diosbulbin B, derived from *D. bulbifera* roots (Huang-yao-zi) are responsible for liver toxicities, nausea, abdominal pain, coma and even death. Oral administration of decoction (400 g/kg) in male Sprague–Dawley rats for 72 h, exhibited elevated levels of taurine, creatine, betaine, dimethylglycine (DMG), acetate and glycine. On the contrary, a reduction in the levels of succinate, 2-oxoglutarate, citrate, hippurate and urea was observed. Marked increase in the organ coefficients of liver and kidney of rats was noticed on exposure to Huang-yao-zi. Histopathological alterations of liver included diffuse hepatocyte degeneration, apoptosis, necrosis in addition to ballooning degeneration of hepatocytes and vascular congestion of hepatic sinusoidal and portal areas. Impairment of mitochondrial energy metabolism indicated by reduction in citrate, 2- oxoglutarate and succinate levels coupled with inhibition of ornithine cycle and urea production confirmed oxidative injury of hepatic mitochondria leading to inhibition of ATP formation resulting in further inhibition of hippurate synthesis. Similarly, elevation in taurine levels due to glutathione depletion also indicated oxidative hepatic damage [44]. Another study, revealed that ethyl acetate fraction (EF) of hydroalcoholic extract of *D. bulbifera* rhizome from China exhibited dose dependent hepatotoxicity in ICR male and female mice when administered consecutively for fourteen days. Maximum elevation in levels of biomarkers of liver injury, namely, alanine transaminase (ALT) and aspartate transaminase (AST) were observed at a highest dose of 480 mg/kg. Reduction in the levels of glutathione- related enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione-S-transferase (GST), glutathione reductase (GR) and glutamate-cysteine ligase (GCL) of hepatic tissues of EF treated mice indicated oxidative stress mediated liver injury in mice [45]. Hepatotoxicity against normal human liver cell line L-02 was reported by diosbulbin D isolated from the rhizome of *D. bulbifera* from China. A time and dose dependent manner of reduction in cell viability was shown by the benzene fraction, highest being 4.32% ± 1.87 at a dose of 800 µg/ml. AnnexinV and propidium iodide assay, Hoechst 33258 staining and the occurrence of a sub-G1 peak indicated diosbulbin D mediated apoptosis induction which was further confirmed to be caspase 3 dependent [46].

Traditional food processing techniques were scientifically validated as most efficient for removal of bitter and toxic compounds from *D. bulbifera* tubers collected by aboriginal people from two locations in northeast Arnhem Land, NT, Australia. Bitterness due to presence of 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, can be effectively removed by the traditional techniques like leaching, thereby, rendering palatability to the processed sliced tubers, otherwise described as "cheeky", meaning bitter or poisonous in aboriginal English. 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, diosbulbin D (0.07 mg/g) decreasing it to a very low level under the taste threshold rendering the final food palatable [47].

Conclusions

Since ancient times, *D. bulbifera* is being used in different parts of the world as traditional medicine against several diseases. Numerous studies on its therapeutic potential are accomplished, as it is considered to be a natural treasure of bioactive principles which can be used for production of new medicines with higher efficacy and biocompatibility with least side effects. Recent researches are continuously adding up new attributes to its pre-existing wide spectrum therapeutic window. As detailed in this review, the comprehensive classical compilation of promising medicinal applications, *in-vitro* and *in-vivo* studies on *D. bulbifera* will enable to search for the untapped pool of novel lead compounds. Further intensive study on isolation and identification of novel compounds with antiviral and antibiofilm properties can broaden its horizon against infectious diseases. Similarly, this review will encourage the screening of more compounds from different groups for plasmid curing efficacy and even for synthesis of novel multifunctional nanomedicine by conjugating with nanocarriers towards rational drug designing and targeted drug delivery. Simultaneously, more scientific experimentation can be initiated with different parts of *D. bulbifera* as well as its isolated phytochemicals to generate evidences supporting its traditional applications, deciphering the underlying mechanism and searching for its utility as nutraceuticals.

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