

Pharmacological Activities of *Dioscorea* spp.: A Narrative Review

N. N. Jamaludin¹, A. Mokhtar¹, N. F. Md Jamil¹, H. Muhammad² and W. M. Md Saad^{1*}

¹Centre of Medical Laboratory Technology, Faculty of Health Sciences, Universiti Teknologi Mara, Puncak Alam Campus, 42300 Puncak Alam, Selangor, Malaysia

²Toxicology and Pharmacology Unit, Herbal Medicine Research Centre, Institute for Medical Research, National Institute of Health Complex, Setia Alam, 40170 Shah Alam, Selangor, Malaysia

Pharmacological research has become essential for the development of nature-based drugs to support the claimed therapeutic properties of medicinal plants. *Dioscorea* species are medicinal plants found to have an impressive pharmacological profile. This review aims to compile the pharmacological properties of three *Dioscorea* species, *D. hispida*, *D. alata* and *D. bulbifera* and their derived compounds through scientific findings, mainly focusing on the biological activities. Relevant clinical and preclinical studies on the pharmacological properties of these plants were identified, screened, and analysed. A systematic search using predetermined keywords on electronic databases (Scopus, Springer and ScienceDirect) was conducted. This review found these *Dioscorea* species to possess various pharmacological activities such as anti-inflammatory, antimicrobial, anticancer, antioxidant, anti-diabetic, antihypertensive and estrogenic effects. The plant tubers contain active compounds such as diosgenin that is responsible for anti-inflammatory and anti-diabetic activities in *D. alata* and *D. bulbifera*, respectively. Other compounds like dioscorine, phenolic, flavonoid and terpenoid elucidated from the yam tubers were found to be antimicrobial and showed prominent free radical scavenging effects. The plants demonstrated various pharmacological activities although data on their mechanisms of action is very limited. Therefore, further research is needed to explore the full potential of these plants as future therapeutic medicines.

Keywords: *Dioscorea alata*; *Dioscorea bulbifera*; *Dioscorea hispida*; pharmacological activity; biological activity

I. INTRODUCTION

Medicinal plants are being extensively researched for their phytochemical constituents which have therapeutic effects in treating diseases. *Dioscorea hispida* Dennst (*Dioscoreaceae*) is a climbing plant with a 6-10 mm prickly stem which grows wild in Southeast Asia and Indonesia. The phytochemical contents showed that it mainly consists of alkaloids, phenol, saponin, phytosterols, and terpenoids (Daud Om *et al.*, 2016). Phosphorus is the main mineral found in *D. hispida* and it contains secondary metabolites of alkaloids, terpenoids, steroids, phenols, and diosgenin (Saleha *et al.*, 2018). Dioscorine (C₁₃H₁₉NO₂), an

isoquinuclidine alkaloid is a toxic substance found in *D. hispida* tubers. The best-known part of this yam is its tuber which is water-soluble polysaccharides and contains various nutrient compositions that include water (7.96%), ash (0.49%), protein (5.59%), fat (2.55%), carbohydrates (83.40%), crude fibre (3.19%) and starch (14.61%) (Harijono *et al.*, 2013). *D. hispida* tuber peel is a rich source of phenolics compounds like caffeic acid, chlorogenic acid, p-hydroxybenzaldehyde and methylester of protocatechuic acid (Sheikh *et al.*, 2013). *Dioscorea alata*, a member of the *Dioscoreaceae* family is one of the herbal medicines that is widely cultivated in the tropics for its edible tubers and bulbs. This species is also virtually unknown in the wild

*Corresponding author's e-mail: wanmaz755@uitm.edu.my

except for occasional records. In Southeast Asia where it was first cultivated, it serves as a source of carbohydrate (Anisuzzman *et al.*, 2016; Jumari *et al.*, 2019). It usually appears as a single tuber varying in size and shape and has succulent caudiciform with an underground tuberous root. It is recognised that yam species has the highest yield of tubers which can be stored for longer duration compared to other species. The low sodium content but high potassium and total dietary fibre (TDF) suggest that *D. alata* plays a potential role as a functional food to satisfy consumer needs for fibre and minerals. *Dioscorea bulbifera* is an important herbal medicine that has been traditionally used in Indian and Chinese cultures to treat various diseases. It is derived from the *Dioscoreaceae* family which is commonly known as aerial yam or air potato. This species is native to tropical, temperate and mountainous land as found in Africa, Asia and Australia. According to the air potato (*D. bulbifera*) management plan (2014), the edible tuber varies from one region to another. In Africa, Australia and Nepal, this species has a well textured flesh with distinctly bitter taste while cultivar Asia has a softer sweeter flesh. *D. bulbifera* tuber also contains storage protein that may be suitable for the development of functional food (Osukoya & Kuku, 2020). However, the consumption of these plants is not recommended due to the toxic components such as saponins, oxalates, alkaloids and tannins. Diosbulbin B and 8-epidiosbulin E acetate belong to diterpenoid lactones, a major constituent in *D. bulbifera* that contribute to liver damage (Lin *et al.*, 2015; WU *et al.*, 2020). Despite their toxicity, numerous studies have demonstrated and provided scientific rationale that *Dioscorea* species has higher efficacy, biocompatibility with the least side effects, and the potential to be developed into therapeutic medicine. Therefore, this review on the pharmacological aspects of *Dioscorea* species was made to acknowledge that these yams are not only edible as staple food but have pharmacological potential.

II. MATERIALS AND METHOD

In this review, the pharmacological properties of three *Dioscorea* species, *D. hispida*, *D. alata* and *D. bulbifera* and their derived compounds were compiled based on scientific evidence, with emphasis on their biological activities.

Relevant clinical and preclinical studies on the pharmacological properties of these plants were identified, screened and analysed. A search using predetermined keywords in electronic databases (Scopus, Springer and ScienceDirect) was conducted.

III. RESULTS AND DISCUSSION

A. Phytochemical Constituents in *Dioscorea* spp.

Dioscorea spp. contains carbohydrates which make them staple food in some countries. However, they also have other beneficial chemical compounds that contribute to pharmacological activities. *D. hispida* is a rich source of high-calorie starch that contains vitamins, minerals, and pharmaceutical properties (Nudin *et al.*, 2017). *D. hispida* contains a large amount of carbohydrates, mainly in the form of starch (Saleha *et al.*, 2018). The percentage of carbohydrates in *D. hispida* ranges from 58.3% to 71.9%, making it the second-highest carbohydrate content among *Dioscorea* spp. after *D. alata* (Saleha *et al.*, 2018). The protein content in *D. hispida* is relatively low at 5.59% (Harijono *et al.*, 2013). It is a yam with low profile content along with *D. bulbifera* (Saleha *et al.*, 2018) and is considered a good source of vitamin C compared to other tuber crops. Behera *et al.* (2010) studied the ascorbic acid content in eleven species of *Dioscorea* and reported that the vitamin C content of *D. hispida* tuber is 7.45 mg/100 gm. The percentage of lipid in *D. hispida* is higher than other yams such as *D. bulbifera* and *D. deltoidea*, ranging from 1.99% to 9.36% (Saleha *et al.*, 2018). The lipid content in *D. hispida* is also higher than other tuber crops, with a percentage of 2.55% (Harijono *et al.*, 2013). Moreover, the water content of *D. hispida* sample was in the range of 7.96% to 37.8%, the lowest among the yam species such as *D. bulbifera* (69.5%) and *D. versicolor* (80.2%) (Harijono *et al.*, 2013; Saleha *et al.*, 2018). However, the nutritional compositions may differ when affected by factors such as soil conditions, pH, organic matter, climate, and postharvest handling and storage (Behera *et al.*, 2010; Nugroho & Estyaniana, 2018).

D. hispida is a three-leaved yam best known for its poisonous tuber due to high content of alkaloid. However, it is a tuber crop with the highest starch content and vitamins

with macro and micro minerals, making it a staple food among the people in the east coast of Peninsula Malaysia (Nudin *et al.*, 2017). Dioscorine ($C_{13}H_{19}NO_2$) is one of the most potent alkaloid toxins found in the tuber of *D. hispida* (Panduranga Murthy *et al.*, 2011; Saleha *et al.*, 2018). The secondary metabolites of *D. hispida* mainly consist of alkaloids, terpenoids, steroids, and phenols (Daud Om *et al.*, 2016; Saleha *et al.*, 2018). Dioscorine has suppressive effects on acetylcholine in the nervous system, which was thought to contribute to its poisonous properties (Saleha *et al.*, 2018). Therefore they can only be consumed after the poisonous tubers are removed (Kamaruddin *et al.*, 2020) although they may not be harmful if ingested in a lower dosage (Lokman *et al.*, 2017). Twenty-seven phytoconstituents were found in ethanol extract and ten in butanol extract of *D. hispida* (Daud Om *et al.*, 2016). The removal of toxins can be done by washing and soaking the tubers in salt solutions for several days, drying, heating, or using the latest method, microwave-assisted solvent extraction. This method lowers the extraction time and reduces environmental pollution (Daud Om *et al.*, 2016; Saleha *et al.*, 2018). Various methods including ultraviolet-visible spectrometry, TLC image analysis and LC-MS technique were performed to identify dioscorine alkaloids compounds in *D. hispida* (Kamaruddin *et al.*, 2020; Kresnadipayana & Waty, 2019; Sasiwatpaisit *et al.*, 2014). Based on the TLC densitometry and TLC image analysis, the researchers found that dioscorine content in dried tuber of *D. hispida* was much higher than in fresh tuber (Sasiwatpaisit *et al.*, 2014). Kamaruddin *et al.* (2020) suggested that the usage of sodium chloride solution helped in removing the toxin alkaloid in *D. hispida* tuber in a shorter period to avoid food poisoning. However, dioscorine tuber contents may be varied as it can be affected by various factors including environmental conditions and genetic factors (Nugroho & Estyaniyana, 2018). Plants containing alkaloids were widely used in both traditional and modern medical practices. *D. hispida* tubers were found to have anti-inflammatory activity, antioxidants, hypoglycaemic effect and antimicrobial properties (Hazrin-Chong *et al.*, 2018; Masdar *et al.*, 2020; Panduranga Murthy *et al.*, 2011; 2015).

In *D. alata*, TLC assay showed presence of at least six different phytoconstituents in each ethanol, methanol and

water extract of *D. alata* tuber that includes alkaloids, steroids, fats, fixed oil, flavonoids, tannins, protein and carbohydrate (Saklani *et al.*, 2013). Fluorescent analysis of phytochemical compounds in *D. alata* revealed the presence of saponins, flavonoids, phenols, alkaloids, terpenoids and glycosides in various concentration. Water is the best solvent to extract these bioactive compounds (Dsouza *et al.*, 2019). Total phenolic and flavonoid content of *D. alata* tuber was confirmed by Sakthidevi and Mohan (2013) where the total phenolic content in methanol extract was found to be 0.68 g 100 g⁻¹ using Folin-ciocalteu method. Total flavonoids content determined using Aluminium chloride method was found to be 1.21 g 100 g⁻¹. Phytochemical analysis of tuber extracts confirmed the presence of alkaloids, tannins, phenolics, glycosides, saponins, resins, terpenoids and anthraquinones (Viji *et al.*, 2016). However, there is difference in the polyphenol content of *D. alata* peels and flesh. The higher content of bioactive components in peel might be the reason for the peel extract to exert better biological activity than the flesh extract (Guo *et al.*, 2015). The study conducted by Hsu *et al.* (2017), identified β -sitosterol, stigmasterol, 22-23-dihydro-, and γ -sitosterol as the major phytosterols in *D. alata*. Estrogenic compounds, hydro-Q9 chromene, γ -tocopherol-9, RRR- α -tocopherol, coenzyme Q9 and 1-feruloylglycerol were identified from ethyl acetate extract of *D. alata* using NMR and mass spectrometry (Cheng *et al.*, 2007). *D. alata*, in each of its variants, contains a beneficial physiochemical. In fact, mineral composition contained in it may potentially contribute to the improvement of human health when consumed adequately (Dufie *et al.*, 2013). Isoforms of dioscorine from the tuber namely DREB 1A (a transcription factor), caffeic acid 3-O-methyl-transferase and Rab-1 small GTP binding protein have been associated with oxidative stress, carotenoid synthesis and vesicular transport in plant. This finding shows that *D. alata* phytochemical compound has yet to be fully explored and exploited. Only a few phytochemical constituents that exists in *D. alata* have been acknowledged. In fact, essential steroidal sapogenin present in *D. alata*, diosgenin, has been widely used in conventional medicine, leading to preclinical and mechanistic studies to better understand and validate its function in pathologies (Dsouza *et al.*, 2019). Thus, there is a need for the other

phytochemical constituents from the yam to be isolated and evaluated for their biological activities.

B. Pharmacological Activities

1. Antioxidant Activity

Plants containing antioxidant properties have been acknowledged for their competency in treating oxidative stress-related diseases. Natural antioxidants primarily originate from plants in phenolic compounds such as flavonoids, phenolic acids and others (Panduranga Murthy *et al.*, 2015). The mechanism is mainly associated with enhancing the defence system in the body by regulating free radicals (Tsai *et al.*, 2009). *D. alata* is one of the fourteen vegetables found to have high antioxidant activity (>70%) evaluated using β -carotene bleaching coupled with oxidation of linoleic acid. A study conducted by Kaur and Kapoor (2002) found positive correlation between antioxidant activity and phenolic content. They suggest that although vegetables have other antioxidant compounds, they do not contribute significantly to antioxidant activity (Kaur & Kapoor, 2002). A positive correlation was also found between total phenol, flavonoids, proanthocyanidins content and radical scavenging activity of the ethanolic and water extract of *D. alata in vitro* (Narkhede *et al.*, 2013). Antioxidant activities derived from purple yam flour positively correlated with anthocyanins and phenolic compounds in the plant based on %RSA and FRAP method (Tamaroh *et al.*, 2018). This study also discovered methanol/HCl as the best solvent to be used in the extraction of anthocyanins from purple yam with high antioxidant activity. Yellow and purple-fleshed yams were found to have significantly higher antioxidant activity compared to white and pink-fleshed yam, estimated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and FRAP assay (Jose *et al.*, 2019). This finding positively correlated to the phenolic, flavonoids and pigment expression using spectrophotometric assay. Although white fleshed yam was widely used, the study revealed that cultivation of purple and yellow-fleshed yam has better nutrient content than white fleshed yam as anthocyanin, phenol and flavonoids derived from plants were known to possess various therapeutic activities. Anthocyanin of the flavonoid group is

responsible for the water and vacuolar pink, red purple and blue pigment present in coloured plants. These contribute to their agronomic value yet they are vulnerable as they could easily degrade and fade when exposed to light (Mahmad *et al.*, 2018). The underground tuber of *D. alata* have higher phenolic content than aerial tuber and better protection against reducing power and hypochlorous acid damage at lower doses (Chatterjee *et al.*, 2012). Hence Chatterjee *et al.* (2012) suggests further isolation of compounds in both aerial and underground tuber in evaluating antioxidant activities mechanism. Based on previous literatures, phenolic compound gives significant attribution in the antioxidant activities of this plant. Moriya *et al.* (2015) found compound 5 with cyanidin skeleton and two sinapic acid units in its structure. This indicated the highest antioxidant activity among all the isolated anthocyanins from *D. alata*. The result suggested the mechanism of action derived from B ring glucosylation at 3'-OH position and presence of acylation or catechol moiety at B ring are positively affected antioxidant activity of the compound in ORACFL assay and FRAP assay, respectively. Purple yam was found to have effect with MGO, a precursor and intermediate of AGEs that induces oxidative damage in HepG2 cell by strengthening the antioxidant defence system. Guo *et al.* (2015) ruled out that both peel and flesh extract of *D. alata* has cytoprotective effect on methylglyoxal (MGO)-induced oxidative damage in HepG2 cells. The researchers proposed that sinapic acid and ferulic acid were compounds that contribute to excellent antioxidant properties. A similar study also reported that synergistic effect of caffeic acid and higher amount of ferulic acid in *D. alata* exerted better antioxidant activity where both compounds were acknowledged to have the most effective radical scavenging (Zhang *et al.*, 2018).

Previous *in vivo* study also indicated that daily intake of dioscorin from *D. alata* lowered oxidative stress and restored learning memory in D-galactose-induced BALB/c mice (Han *et al.*, 2014). Increased glutathione (GSH) content and oxygen radical absorbance capacity (ORAC) activity with decreased malondialdehyde (MDA) content and inducible nitric oxide synthase (iNOS) protein expression showed that learning dysfunctions in mice can be improved by dioscorine intervention via reduction in oxidative stress.

This *in vitro* antioxidant activity was proposed to be exhibited by the peptides or amino acid synthesised from peptic hydrolysate of dioscorine. Higher GSH level and oxygen radical antioxidant capacity activity with lower MDA and iNOS level in mice brain compared to the control group reflects traditional juvenescent use of this plant with anti-aging potential treatment. Besides, no cytotoxicity effect was observed towards primary HUVEC cells *in vivo* (Han *et al.*, 2014). *D. alata* supplementation also recovers oxidative stress in different regions of the brain induced by hyperhomocysteinemia (HHcy). The study result showed a decline in homocysteine (Hcy) and MDA plasma level compared to methionine-induced group, indicating that this plant has protective action against lipid peroxidation and HHcy (Tsai *et al.*, 2009). The researchers stated that depleted GSH level in striatum was markedly restored possibly due to high synthesis of GSH by amino acid precursor in *D. alata*. This suggests the plant's potential as the treatment of oxidative-related degenerative neurological disorder like Parkinson disease. Similar findings can be seen in reversed hepatic ROS production by *D. alata* feeding in methionine-induced HHcy in rat based on decline in platelet aggregation and plasma MDA level which was the indicator of lipid peroxidation (Chang *et al.*, 2004).

Pepsin hydrolysis of yam dioscorin derived thiol-containing diotides exhibit hydroxyl radical scavenging activities, have anti-lipopolysaccharide (LPL) peroxidation properties, anti-AAPH-induced hemolysis activity, oxygen radical absorbance capacity and protective abilities against MGO-induced cell death in HUVEC cell model (Han *et al.*, 2013). Glutathione peroxidase (GPx) activity was proposed to be the protective mechanism involved against *tert*-butylhydroperoxide-induced oxidative cell in both Hepa 1-6 and FL83B mouse liver cell using ethanolic extract of *D. alata* peel (Hsu *et al.*, 2011). Higher antioxidant activity was observed in water soluble polysaccharides (WSP) extracted from purple yam compared to yellow yam (Estiasih *et al.*, 2018). A study suggests that the result was due to the combination of dioscorine and other reducing compounds like anthocyanin (pigment) extracted during the preparation of crude WSP. This review indicated that the presence of dioscorine in crude WSP extract in purple yam have high yield protein content compared to yellow yam. Besides,

Sakthidevi and Mohan (2013) showed that ethanol extract of *D. alata* tuber indicated positive antioxidant activities and strong DPPH scavenging activity *in vitro*. The tuber extracts of *D. hispida* was found to exhibit potent antioxidant activity (Han *et al.*, 2014; Masdar *et al.*, 2020; Miah *et al.*, 2018; Murthy *et al.*, 2017). Han *et al.* (2014) reported that the synthesised peptides extracted from dioscorine peptic hydrolysates exhibited *in vitro* antioxidant activities.

Methyl-3,4-dihydroxybenzoate, one of the phenolic compounds isolated for the first time from *D. alata* tuber has higher antioxidant activity (IC₅₀: 9,41 ppm) than the positive control ascorbic acid and the other compounds found in plant, 9,10-dihydrophenanthrene-2,4,7-triol (Aminah *et al.*, 2017). Myricetin, a flavonoid was proposed to contribute to the antioxidant and reducing power activity possessed by *D. alata* bulb (Anisuzzman *et al.*, 2016). The extract showed stronger antioxidant properties (IC₅₀=14.68 µg/mL) than to the standard antioxidant ascorbic acid (IC₅₀=24.95 µg/mL) in DPPH assay and comparable reducing power with maximum absorption of 1.317 compared to standard BHT of 1.472 at 1 mg/mL. Although flavonoid is a well-known antioxidant, there is a need to confirm myricetin and other phenolic compound contribution in antioxidant activity.

There were similar findings found from phenolic compound attribution to antioxidant activity in *D. hispida*. The phenolic compounds in *D. hispida* may produce significant antioxidant activity as it prominently scavenged the DPPH free radicals (Miah *et al.*, 2018). It has antioxidant and anti-inflammatory activities, which can be related to the antiphlogistic effects of the steroidal saponins (Napisah *et al.*, 2011). *D. hispida* was found to have a noticeable amount of phenolic content and showed a prominent free radical scavenging effect. Alkaloids, phenols, saponins, phytosterols and terpenoids were mostly found in the tuber of *D. hispida* (Daud Om *et al.*, 2016). These might be linked to the membrane stabilisation and anti-inflammatory potentials of the plant (Miah *et al.*, 2018). The production of free radicals can be linked to several diseases, including cell mutagenesis, cancer, atherosclerosis, diabetes, and inflammatory diseases (Santos-Sánchez *et al.*, 2019). An alkaloid called dioscorine present in the tuber of *D. hispida* and steroidal saponin delivered an effective antioxidant

which showed anticancer activities (Panduranga Murthy *et al.*, 2015). The free radical scavenging ability of *D. hispida* could be linked to its dioscorine content (Masdar *et al.*, 2020; Miah *et al.*, 2018; Murthy *et al.*, 2017). The cyclic chain with nitrogen bonding to the carbon group (C-N) in the dioscorine compound contributes to the antioxidant ability of *D. hispida* (Masdar *et al.*, 2020). Analysis showed that there is a link between total active phytochemicals with phenolic and flavonoid material, as well as radical scavenging activity with anti-proliferative breast cancer activity (Murthy *et al.*, 2015). The studies not only paved the way for a tentative contribution to the investigation into medicinal botany but also showed a way for future pharmacological studies to discover new sources of medicinal products extracted from these phytochemicals (Sheikh *et al.*, 2013).

2. Antidiabetic activity

Diabetes mellitus is known to be a serious multifactorial metabolic disorder characterised by hyperglycemia and impaired metabolism of carbohydrates. Multiple biochemical impairments associated with micro- and macrovascular complications such as hyperlipidemia, retinopathy and cardiovascular diseases are causal factors towards morbidity and death. Most *D. alata* variants had higher total dietary fibre (TDF) value due to starch content. This species has been studied for antidiabetic treatment as TDF was known to affect viscosity of the yam flour (Dufie *et al.*, 2013). Similar finding was reported where *D. alata* variety, 'Uwi Ungu Kudus' as known in Indonesia, contains high amount of amylopectin useful for treating diabetic related problem as it has viscous property compared to amylose that has grainy character. Jumari *et al.* (2019) agree high amylose generates grainy character while high amylopectin produces sticky character. Two active compounds in *D. alata*, water soluble polysaccharides and anthocyanin were found to lower blood glucose in hyperglycaemia condition. Soluble polysaccharides can form viscous mass in solution and influence the properties of mucilage extracted from the yam. Increased viscosity from the soluble polysaccharides was believed to be the mechanism that caused decline in blood glucose level. This condition was effective in suppressing post-prandial high

glucose as glucose transportation was hindered by high resistant of mucosal diffusion (Estiasih *et al.*, 2018).

Ethanol extract of *D. alata* tuber show antihyperglycaemic effect in alloxan induced diabetic rat but did not produce hypoglycaemic effect in normal, fasting rat and show significantly reduce of blood glucose in normal rat. Blood glucose reduced significantly with serum lipid levels, total protein, albumin and creatinine were all reversed towards near normal in diabetic rat compared to control mice. Flavonoid was suggested to induce the antihyperglycaemic effect, yet more thorough research is needed to elucidate the mechanism of action (Maithili *et al.*, 2011). Ethyl acetate extract of peel and flesh from *D. alata* exhibited excellent antiglycation ability by suppressing glycation cascade stages with antioxidant activities as their main underlying mechanism. It is proposed that sinapic acid and ferulic acid compound contributed to the excellent antiglycation properties in this plant (Guo *et al.*, 2015).

Several studies reported that *D. bulbifera* extracts (DBE) has a potent antihyperglycaemic activity that significantly reduced blood glucose level (Ahmed *et al.*, 2009; Igbokwe *et al.*, 2017). 500 mg/kg p.o and 1000mg/kg p.o of DBE produced significant antihyperglycaemic effects ($P < 0.001$). However, the effect was not superior to glibenclamide (0.5 mg/kg p.o glibenclamide) (Ahmed *et al.*, 2009). Moreover, *D. bulbifera* amala flour samples significantly ($p < 0.05$) reduced fasting blood glucose level from 645 to 75.67 mg/dl compared to the diabetic control group (Igbokwe *et al.*, 2017).

Pancreatic and intestinal enzymes break down carbohydrate and lipid into smaller particles for it to be easily absorbed through intestinal mucosa, thus inhibiting this enzyme to slow down uptake into blood circulation. Diosgenin in *D. alata* was found to delay glucose diffusion and inhibit these key metabolic enzymes with maximum inhibition concentration, on par with the positive control of commercial inhibitor enzymes, Acarbose (amylase) and Orlistat (lipase). It was proposed that diosgenin would be able to replace metformin in treating Polycystic Ovary Syndrome (PCOS) and metabolic related diseases like hyperglycaemia and obesity. The compound produced similar effect as biguanide, yet it did not show any side effects of irritation within the gastrointestinal region. It was

also found to have a distinctive similar structure as estrogen which helps in treating PCOS, thus giving the compound 'Triple Effect' (Dsouza *et al.*, 2019). Guo *et al.* (2015) corroborate that ethyl acetate fraction of *D. alata* extract also inhibit diabetes key enzyme, α -amylase and α -glucosidase, as well as non-enzymatic glycation that leads to diabetic complications. The extract could also alleviate free fatty acid (FFA)-induced insulin-resistant in HepG2 cell which is highly proposed to be functioned through their antioxidant activities.

One of the serious complications in diabetes is postprandial hyperglycaemia (PPHG). It is a condition where blood glucose level remains high after consuming meals due to α -glucosidase and α -amylase activities. One of the therapeutic methods in regulating PPHG in diabetic patients is to suppress the carbohydrate-digesting main enzymes by inhibiting their activity using α -glucosidase and α -amylase inhibitors. Thus, a study by Ghosh *et al.* (2014) was carried out to investigate inhibitory effects of *D. bulbifera* bulbs extracts against α -amylase and α -glucosidase enzymes. The enzymes were derived from pancreas, liver and small intestine tissues of Swiss mice that had been excised and homogenised with appropriate reagent. In *D. bulbifera*, four different extracts, petroleum ether, ethyl acetate, methanol and 70% ethanol, were prepared to evaluate which extract worked more effectively. The result of α -amylase and glucosidase inhibition assays found that extracts of methanolic *D. bulbifera* (73.64%) were potent inhibitor against porcine pancreatic α -amylase compared to petroleum ether (61.65%) and ethyl acetate (73.39%) extracts. Moreover, petroleum ether extracts of *D. bulbifera* showed 73.3% glucosidase inhibition against murine liver glucosidase enzyme and was most significant among the plant extracts. A HPLC Fingerprinting test was done to discover marker compounds and their phytochemical profile present in the plant extracts. The test presented high content of diosgenin in the methanol extracts of *D. bulbifera* bulbs (Chopade *et al.*, 2012).

Diosgenin is a steroidal saponin derived from several plants which exhibits much potential in biological activities, with increasing interest in the pharmaceutical industry. Similar to *D. alata*, *D. bulbifera* is also known to contain saponins called diosgenin (Ghosh *et al.*, 2014; Ghosh *et al.*,

2015). It is believed to be a novel hit treatment for PPHG of type II diabetes mellitus due to their inhibitory activity against α -amylase and α -glucosidase (Ghosh *et al.*, 2014). As a continuation from their previous study, Ghosh *et al.* (2014) provided solid evidence to prove *D. bulbifera*'s inhibitory activities against α -amylase and α -glucosidase. Their research provided further investigation in isolation, structural elucidation, inhibitory activity and kinetics of active components present in *D. bulbifera* against pancreatic α -amylase and α -glucosidase. Among other extracts, ethyl acetate extract was found to be more potent in inhibition activities. Thus, GC-TOF-MS test was done on extracts that showed maximum activity and found that diosgenin is a major phytoconstituent present in ethyl acetate extract. Compared to the crude starting source, HPTLC of the HPLC purified the compound D verified the single compound purity close to standard diosgenin. Ethyl acetate extracts of *D. bulbifera* showing maximum inhibition in porcine pancreatic amylase ($72.06 \pm 0.51\%$) equivalent to compound D ($70.94 \pm 1.24\%$), same as inhibition in crude murine pancreatic amylase ($37.28 \pm 1.6\%$) and $39.56 \pm 3.02\%$ in compound *D. bulbiferous*. Glucosidase inhibition activity, ethyl acetate extract exhibited excellent activity of $71.15 \pm 2.9\%$ followed by compound D ($67.61 \pm 1.31\%$). Glucosidase inhibition in crude murine intestinal was in agreement with pure α -glucosidase inhibition assay result. In kinetic analysis of inhibition activity compound D, decreased K_m and V_m indicated uncompetitive mode of inhibition. However, decrease in fluorescence intensity confirmed interaction of D with α -amylase. Next, changes in secondary structure of α -amylase were observed using CD spectrometry and this confirmed the interaction between compounds D with active site of α -amylase. Molecular docking studies were carried out which indicated interaction in hydrogen bonding between Asp300 residues of α -amylase with Tyr62, Trp58, Trp59, Val163, His305 and Gln63 residues responsible for hydrophobic binding. Glucosidase Asp352 and Glu411 residues interacted with diosgenin (Ghosh *et al.*, 2014).

3. Antihyperlipidemic

In diabetes mellitus type 2, hyperglycaemia always accompanied dyslipidemia which is one of the major risk

factors for cardiovascular disease in diabetic patients. It is characterised with high plasma concentration of triglycerides, low density lipoprotein (LDL), very low density lipoprotein (VLDL) and total cholesterol, with decrease in high density lipoprotein (HDL) concentration. *D. bulbifera* extracts are reported to be antihyperlipidemic by decreasing concentration of LDL, VLDL and total cholesterol, and recover low levels of HDL by increasing their concentration (Ahmed *et al.*, 2009; Chinko *et al.*, 2020). Chinko *et al.*'s study (2020) showed total cholesterol, triglycerides, low density lipoproteins, very low density lipoproteins, serum glucose. Besides, atherogenic index were found to be significantly lower in treated groups with 200 mg/kg of DBE compared to untreated hyperlipidaemic rats ($P < 0.005$) (Chinko *et al.*, 2020). This observation is in close agreement with Ahmed *et al.* (2009) whereby the lipid profile improved. TG, TC and LDL were reduced, and HDL increased significantly ($P < 0.001$) in high fat diet fed mice treated with 500 and 1000 mg/kg p.o. doses of DBE. It is also found that antidyslipidemic effect of 1000 mg/kg p.o. of DBE corresponded to the 300 mg/kg p.o. of fenofibrate, which is the drug used to treat hyperlipidemia. Although DBE concentration is quite high and might cause side effects due to toxicity, it is proven to be safe throughout the study period whereby rat treated with 2000 mg/kg DBE did not show any physical signs of toxicity or death (Ahmed *et al.*, 2009).

4. Antimicrobial activity

D. hispida has an antimicrobial activity that functions to kill or stop the growth of microorganisms (Azman *et al.*, 2016; Hazrin-Chong *et al.*, 2018; Miah *et al.*, 2018; Napisah *et al.*, 2011; Panduranga Murthy *et al.*, 2015). A part of toxic alkaloids containing a large amount of nitrogen known as dioscorine is responsible for producing antioxidant ability and antibacterial properties against specific bacteria species (Azman *et al.*, 2016). Dioscorine was found to be present with steroidal sapogenins suggesting that it may be involved with this biological activity (Panduranga Murthy *et al.*, 2015). It shows the ability to inhibit certain groups of bacteria and fungi (Azman *et al.*, 2016; Kartini *et al.*, 2018; Miah *et al.*, 2018). Various amounts of phenolic contents in the tuber of *D. hispida* have been demonstrated to be

antibacterial based on several mechanisms (Hazrin-Chong *et al.*, 2018). Napisah *et al.* (2011) found that the tuber extracts of *D. hispida* were effective against *S. aureus*, *B. cereus*, *C. albicans*, and *E. coli* at high concentration of extracts. It also showed high susceptibility to gram-positive bacteria such as *S. aureus* and *B. subtilis*, and other gram-negative bacteria including *E. coli*, *P. aeruginosa*, and *K. pneumoniae* (Hazrin-Chong *et al.*, 2018; Panduranga Murthy *et al.*, 2015). Kartini *et al.* (2018) demonstrated that the tuber extract was able to produce minimal inhibition growth of *Pleomorphomonas oryzae*. These prove that *D. hispida* has the ability to inhibit specific groups of bacterial and fungal pathogens (Azman *et al.*, 2016; Miah *et al.*, 2018). Flavonoids, a hydroxylated phenolic compound, known to be synthesised by plants in response to microbial infection and are an antimicrobial agent against a wide array of microorganisms *in vitro*. This is due to their ability to complement extracellular and soluble proteins with bacterial cell wall present in *D. hispida* tuber (Nugroho & Estyaniyana, 2018; Panduranga Murthy *et al.*, 2015). It is also one of the alkaloids that may exert antimicrobial activity of *D. hispida* with steroids (Panduranga Murthy *et al.*, 2015). The phenolic compounds are able to inhibit microbial pathogens via various mechanisms including growth inhibition, cytological damage and mutagenic reaction (Miah *et al.*, 2018). The established phytochemical compounds may be bioactive components and therefore these plants are proving to be increasingly valuable reservoir of bioactive compounds of significant medicinal value (Murthy *et al.*, 2017; Panduranga Murthy *et al.*, 2015). However, further studies regarding this matter is needed to clarify the chief active constituents responsible for *D. hispida* antimicrobial activity and the performance of *D. hispida* when combined with antibiotics (Hazrin-Chong *et al.*, 2018).

Multidrug resistant (MDR) bacteria pose significant public health risk due to their ability to infect individuals without causing symptoms. They can endure harsh environments and grow resistance towards antibiotics. In a research by Dahiya (2017), aqueous and chloroform extracts of *D. bulbifera* were found to be more potent in inhibition activity against bacteria. Highest inhibition zones were observed in *K. pneumoniae* (17 ± 0.15 mm), *E. coli* (13 ± 0.11 mm) and

Acinetobacter spp. (11 ± 0.12) compared to methanol and ethanol extracts that did not show any inhibition zone on the tested organism (Dahiya, 2017). On the contrary, Adeosun (2016) and Enwani (2017) reported no inhibitory activities in aqueous extracts of *D. bulbifera* (Adeosun *et al.*, 2016; Enweani, 2017). This is possibly due to water not being able to penetrate deep enough to extract the phytochemical constituents present in deeper tissues, and the compounds may not be water soluble (Enweani, 2017). Kuete *et al.* (2012) reported that methanol extracts and their six isolated compounds showed excellent inhibitory against MDR microorganisms and some strains of mycobacteria. Methanol crude extracts, DBB1 and DBB2 fractions and compound bafoudiosbulbins B, C, F and G are able to inhibit the growth of *E. coli*, *E. aerogenes*, *K. pneumoniae* and *P. aeruginosa* of different strains. In addition, they can also inhibit the growth of *M. tuberculosis* MTCS2 and ATCC strains. However, the most prominent compound is bafoudiosbulbins C which is able to inhibit the growth activity of the three of the four tested mycobacterial strains (*M. smegmatis* and *M. tuberculosis* ATCC, MTCS1 and MTCS2 strains). Phenylalanine arginine β -naphthylamide (PA β N), also known as efflux pump inhibitor, is used to rejuvenate activities of antibiotics against bacteria pathogen that develops resistances towards antibiotics. The combination of isolated compounds from *D. bulbifera* and PA β N showed an increase in inhibitory activities against tested bacteria. The application of inhibitors with combination of active compounds extracted from *D. bulbifera* as a substrate against efflux pump of MDR bacteria can be potential mechanisms to combat these strains (Kuete *et al.*, 2012).

Phytochemical analysis of tuber extracts of *D. alata* confirmed the presence of alkaloids, tannins, phenolics, glycosides, saponins, resins, terpenoids and anthraquinones which produced positive results in antimicrobial activity besides expressed cytotoxicity against Dalton's lymphoma ascites (DLA) cell ascertained using Trypan blue method. However, specific chemical constituents that act on the activity mentioned has yet to be identified (Viji *et al.*, 2016). Other studies revealed that anthocyanin extracted from *D. alata* showed antibacterial activity *in vivo* and *in vitro* against *Escherichia coli* with highest inhibition zone *in vivo*

(8.8 mm) followed by *in vitro* extract (7.8 mm) (Mahmad *et al.*, 2018). The extract of *D. alata* bulb exhibited antibacterial activity based on significant zone of inhibition against all experimental bacterial strains used except for *Staphylococcus epidermidis*. However, further study is needed to confirm the contribution of myricetin and other phenolic compound actions on this antibacterial activity (Anisuzzman *et al.*, 2016).

Other than compounds found in the plant itself, *D. alata* mediated silver nanoparticles also showed antimicrobial activity confirmed by agar well diffusion method with zone of inhibition of synthesised nano particles higher than the plant extract. This is due to the differences in local electronic structure on the surface of smaller size particles that enhanced their chemical reactivity and bactericidal effects. The antibacterial activity of nanoparticle is more effective against gram negative bacteria (*Escherichia coli*) than gram positive (*Staphylococcus auricularis*) ones due to variations in cell wall composition. Nanoparticles accumulate inside the membrane and subsequently penetrate the cell as positively charged nanoparticle attracted negatively charged bacteria cell. More nanoparticle mediated research needs to be done in the future to confirm its effectiveness compared to plant extracts (Pugazhendhi *et al.*, 2016).

5. Synthesis of nanoparticles

Nanoparticles derived from plants have been gaining popularity due to its eco-friendly nature and cost-effectiveness. These particles produce a wide range in medicinal use such as antibacteria, anti-parasite, anticancer and antioxidant (Ghosh *et al.*, 2015). Some of the most studied metallic nanoparticles include silver (Ag) (Ghosh *et al.*, 2012; Ghosh *et al.*, 2015), gold (Au), platinum (Pt), and palladium (Pd) (Ghosh *et al.*, 2015). Due to its unique phytochemistry, *D. bulbifera* was found to be synthesised into gold, silver, platinum and palladium nanoparticles. The rapid synthesis of Au@Ag shell NPs was achieved within 5 hours with diameter between 5 and 11 nm of inner core and 13 to 19 nm of whole particle. The size was found to be monodispersed with spherical shape with dark contract core surrounded by lighter shades of shells. EDS analysis confirmed the presence of silver and gold particles which contain $57.34 \pm 1.01\%$ gold and $42.66 \pm 0.97\%$ silver of the

total mass (Ghosh *et al.*, 2015). A similar study by Ghosh *et al.* (2015) also showed rapid synthesis of bimetallic nanoparticles within 5 hours. The nanoparticles comprised 30.88%±1.73% elemental Pt and 68.96%±1.48% elemental Pd. In fact AuCoreAgshellNPs derived from *D. bulbifera* is able to inhibit biofilm formation of *A. baumannii* (83.68±0.09%) effectively at concentration of 100µg/mL, followed by *E. coli* (22.33±0.56%), *S. aureus* (30.70±1.33%) and *P. aeruginosa* (18.93±1.94%). This activity was confirmed with the presence of irregular morphology due to cell damage, discreet cells, significant membrane disintegration and surface invaginations. The complete loss of spindle shaped morphology of *L. donovi* into spherical ones was observed and confirmed the effect of AuCoreAgshellNPs in antileishmanial activity (Ghosh *et al.*, 2015). Moreover, a combination of silver nanoparticles with antibiotics can enhance antimicrobial activities. *K. pneumoniae*, *P. mirabilis* and *P. aeruginosa* are resistant in the presence of vancomycin alone. However they were found to be inhibited after a combination of vancomycin with silver nanoparticles (Ghosh *et al.*, 2012). In anticancer activity, Pt–PdNPs demonstrated high toxicity activity against HeLa cells (74.25%) compared to individual PdNPs (33.15%) and PtNPs (12.6%). This might be due to the synergistic effects of both components that have become more potent (Ghosh *et al.*, 2015). Antioxidant is an important chemopreventive agent against cancer. Pt–PdNPs showed excellent antioxidant activity by scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH), superoxide, nitric oxide, and hydroxyl radicals (Ghosh *et al.*, 2015).

6. Immunomodulatory activities

Inflammation involves several mediators such as cytokines, free radical, nitric oxide (NO) neutrophil derived free radical, prostaglandins and reactive oxygens species (ROS). Overproduction of these mediators can lead to tissue injuries by lipid membrane peroxidation and damage to the macromolecular tissues (Dsouza *et al.*, 2019). Hydromethanol extract of *D. alata* tuber significantly downregulate pro-inflammatory cytokines gradually by inhibiting NO and TNF-α expression (IC₅₀=134.51). This result correlates with the decline in PGE₂ level and COX-2 activity (R²=0.9393) (Dey *et al.*, 2016). The finding was

supported by the synergistic activities of the phytochemical constituents present that also attributed to the anti-inflammatory activity in this plant. Bioactive compounds identified were gallic acid, 4-hydroxy benzoic acid, syringic acid, p-coumaric acid and myricetin characterised using HPLC techniques while GCMS analysis revealed thirteen different phytochemicals including hexadecenoic acid, methyl stearate, cinnamyl cinnamate and squalene. Similarly, methanolic extract of *D. alata* aerial tuber (DATE) proved to improve humoral immunity, facilitate macrophage activity against foreign pathogen and act as potent anti-inflammatory agents (Dey *et al.*, 2016). DATE downregulates pro-inflammatory cytokines (IFN-γ, TNF-α, NO, IL-2, COX-2 and PGE₂) while upregulating anti-inflammatory cytokines (IL-4, IL-10) to promote the proliferation of T_{H0} immune responds towards T_{H2} phenotype. Declining in cell adhesion property helps to reduce macrophage recruitment and hinders the release of proinflammatory cytokines to injury site. Myeloperoxidase (MPO) released and respiratory burst activity able to kill internalised pathogen is evidence that DATE can modulate murine macrophage to be protective against tissue damage and microbial infections. Phytochemical constituents identified in HPLC analysis and GCMS include myricetin, vanillic acid, gallic acid, palmitic acid, linoleic acid and squalene, which were suggested to have profound influence on the immunomodulatory properties (Dey *et al.*, 2016). In contrast, a study showed *D. alata* underground tuber actively polarise T_{H0} lymphocyte to proliferate towards T_{H1} immune response expression by upregulating IFN-γ and IL-2 expression and downregulating IL-4 and IL-10 expression through ELISA *in vitro* (Dey & Chaudhuri, 2014). This hydro-methanolic extract of *D. alata* underground tuber also possessed mitogenic activity by stimulating splenic T-lymphocyte proliferation *in vitro*.

Dioscorin isolated from *D. alata* can induce TLR-4 downstream cytokine expression in bone marrow cell of TLR-functional C3H/HeN mice and stimulated multiple signalling molecules and induced signalling of cytokines in murine RAW 264.7 macrophages (Fu *et al.*, 2006). Therefore, this study determined dioscorin as a novel TLR-4 activator that induced macrophage activation via typical TLR-4 signalling pathway. Cytokine production and iNOS

expression in macrophage cell line was stimulated which indicate dioscorin treatment may lead to macrophage activation to eliminate pathogen in innate immune response and activate TH cell for adaptive immunity (Fu *et al.*, 2006). Different mouse strains responded differently to immunomodulatory effects of dioscorine because in RAW264.7 macrophages, TNF- α , IL-1 β , IL-6, IL-1-, RANTES, MCP-1 and GCSF gene expression were upregulated whereas in BALB/c and C57BL/6 models, gene expression of TNF- α , IL-1 β , IL-6, IL-1- and RANTES were higher in spleen cell compared to bone marrow and thymus cells (Hsu *et al.*, 2015). This suggests that the regulation of various cytokine expressions during immune response would be a reasonable strategy in treatment using dioscorine for immune related diseases in the future. Purified dioscorin from *D. alata* tuber acted as immunomodulatory substance that stimulated both NO and cytokine productions, and enhanced phagocytosis in macrophages (Lu *et al.*, 2012). This *in vitro* study was previously conducted with *in vivo* test in animal model done by Liu *et al.* (2009). Ingested dioscorin was found to enhance phagocytosis activity and NK activity in BALB/c model. Increased NK cell subpopulation in peripheral blood and spleen cell was probably due to elevated IFN- γ which eventually stimulated splenocyte-mediated NK activity. Besides, oral dioscorin *in vivo* also increased number of Peyer's patches which enhance proliferation of lymphocyte and elevate secretion of IgA (Liu *et al.*, 2009). Active peptides with immunomodulatory activity from dioscorin hydrolysate should be isolated to evaluate the compound responsible in this mechanism. Besides that, TN-1 dioscorins from *D. alata* has better ability in modulating phagocytic activity of lymphoid cell against *E.coli* compared to *D. japonica in vivo* (Lin *et al.*, 2009).

Diosgenin from water extract of *D. alata* was revealed to possess anti-inflammatory property with optimal inhibitory activity of (IC₅₀= 0.16 μ g/mL) comparable to aspirin (IC₅₀= 1.76 μ g/mL) (Dsouza *et al.*, 2019). Ethanolic extract of *D. alata* decreased IgE level in ovalbumin- induced mice with increase in TNF- α expression similar to antihistamine drug dose. The author proposed the flavonoid act as cyclooxygenase inhibitor which reduced pro-inflammatory mediators while phenolic compound binds to the receptor

on lymphocyte to initiate anti-inflammatory response (Makiyah *et al.*, 2014). Newly developed noodles made of yam (*D. alata*) and boxthorn (*Lycium barbarum*) was found capable of elevating IgG and IgA serum level in dose-dependent manner in mouse model. Although the study confirmed that boxthorn polysaccharide has the best immunomodulatory effect on gut, it is assumed that the lectin proteins and mucopolysaccharides in *Dioscorea batatas* were also present in *D. alata*. This combination of food formula was shown to be safe with no toxic effect on the body. The findings indicated that continuous intake of yam-boxthorn noodle can modulate Th1/Th2 balance with favour to Th1, providing the possibility for this new food to exhibit protective immunity and antiallergic activity (Lin *et al.*, 2006). Besides that, *D. hispida* was reported to be anti-inflammatory which also demonstrated prominent thrombolytic activity, which inhibited platelet aggregation of thrombin and oxidised low-density lipoprotein (Miah *et al.*, 2018). The data collected from literature supports the idea that yam has the potential as an immune-promoting medicinal plant.

7. Antiosteoporotic activity

Ethanol extract of *D. alata* rhizome (Dispo85E) was found to have the potential as a candidate drug for osteoporosis therapy (Peng *et al.*, 2011). *In vivo* data revealed that osteoblastogenesis was significantly modulated by Dispo85E with increasing ALP activity and bone nodule formation in both intact and ovariectomised (OVX) mice. Dispo85E was proven *in vitro* to promote bone formation by inducing pluripotent C3H10T1/2 stem cells differentiation into osteoblast rather than adipocyte based on cell viability assessment, thus eliminating concerns on whether the cell would proliferate into cancer. Dispo85E also has anti-adipogenic ability as the extract reduced adipogenic cell differentiation, thus the potential use for hematopoietic disorder. Peng *et al.* (2011) also used an OVX mouse model to mimic the osteoporosis condition common among postmenopausal women. The extract made of *D. alata* was discovered to enhance osteoblastogenesis without giving side effect to the uterine weight after six weeks compared to the usual restorative effect of estrogen replacement therapy. Therefore, Dispo85E has the potential in the treatment of

bone disease without affecting uterus in postmenopausal women (Peng *et al.*, 2011).

8. Antihypertensive activity

Purified dioscorin from *D. alata* Tainong No.1 derived by spectrophotometric method was determined to inhibit angiotensin converting enzyme (ACE) in dose dependent manner using qualitative TLC method. It is also found that the smaller peptides are elevated with the increase of pepsin hydrolytic, therefore dioscorin and its hydrolysate were proposed to have potential for hypertensive-related disease treatment (Hsu *et al.*, 2002). The above-mentioned study was supported with reports on both powdered and liquid-yam products that were found to effectively reduce blood pressure in spontaneously hypertensive rat, therefore oral administration of water extract of yam products may be potential antihypertensive food in the future (Liu *et al.*, 2009).

9. Anticlastogenic, anticancer and antineoplastic activity

The study done by Wang *et al.* (2011) demonstrated that water soluble mucilaginous polysaccharide within aqueous extract of *D. alata* were the protective compound that carry out anticlastogenic activity by acting as the metal copper ions chelator against copper-mediated DNA damage *in vitro*. However, the aqueous extract of *D. alata* protects against ferric-ion induced DNA damage only observed on human lymphoblastoid cells. Besides that, active compounds such as anisaldehyde, sulphuric acid-reactive and highly polar substances were proposed to be involved in the mechanism of anticlastogenic activity compared to polyphenol which turned to be ineffective as it was suppressed with copper-H₂O₂-induced DNA damage. A survey conducted on medicinal plants used for cancer treatment by traditional healers in Africa showed *D. alata* tuber can treat skin cancer yet no literature has been published to support the claims (Agyare *et al.*, 2018).

D. hispida was also found to be the most potential anticancer agent. The integration of the different herbal composition remedy may reduce and lower cancer risks associated with oxidative stress disease (Panduranga Murthy *et al.*, 2011; Wei *et al.*, 2013). Dioscine from the tuber content demonstrated its anticancer properties by

inducing DNA damages, blocking the S phase cell cycle, and activating the mitochondrial signal pathway (Wei *et al.*, 2013).

Cytotoxic activity of compounds is important in inhibiting proliferation of cancer cells. In order to prove *D. bulbifera* is able to antagonise actions of cancer cells, Nur and Nugroho (2018) investigated cytotoxic activities of fractions from chloroform and methanol extracts of *D. bulbifera* against T47D breast cancer cells. The result showed that chloroform extracts have potent cytotoxic activity compared to methanol extracts. Twelve fractions were obtained from fractionation of chloroform extracts using vacuum liquid chromatography. The fractions that have similar profiles were merged and tested for cytotoxic activity whereby five out of six combined fractions had significant cytotoxic activity where their IC₅₀ were less than 100 µg/mL. It is coordinated with the range prescribed by National Cancer Institute (NCI). Furthermore, DBE does not show any cytotoxic effects against normal cells, thus indicating its safe use. Alkaloid and terpenoid compounds were present in potential fractions where alkaloid helps in reducing and antagonising cytotoxic activity of terpenoid (Nur & Nugroho, 2018). Rachaiah *et al.* (2019) concurred the cytotoxic activity and antineoplastic activity of DBE against MCF-7 and murine mammary carcinoma cells. Cytotoxic activity was evaluated by performing proliferation assay on cells against different extracts of *D. bulbifera*. The result showed 60 – 70% of cell death were observed in ethyl acetate, acetone and methanol extracts. With the addition of MTA1 protein into cells, there was a significant decrease in MCF-7 cells proliferation (70-75%) in ethyl acetate and acetone extracts. Presence of membrane blebbing and fragmented nuclei of cells indicated the cells undergo apoptosis. Next, wound healing assays were done to investigate DBE activity in preventing MTA1 induced migration activity of cells. The wound gaps were then observed. Cells treated with ethyl acetate, acetone, chloroform and methanol inhibited the cell migration by keeping the wound open. This can be compared with MTA1 induced cells, where the gap between wounds was gradually narrowed down (Rachaiah *et al.*, 2019). Kaempferol-3,5-dimethylether, caryatin, myricetin and catechin were isolated from DBE fractions. They were

excellent antitumor promoter that inhibited the formation of colony on TPA induced soft agar (Gao *et al.*, 2002).

Angiogenesis is a formation of new blood vessels. Although it plays a normal part in growth and healing, it is also vital to invasion of cancer cells. This neovascularisation provides oxygen and essential nutrients towards developing tumours. It also facilitates tumour metastasis and invasion into nearby normal tissue. A study reported DBE has angiogenic activity by inhibiting formation of new blood vessels. Angio-inhibitory effects were evaluated by performing *in vivo* peritoneal angiogenesis assay. Regressions of neovascularisation were observed in ethyl acetate and acetone extracts compared to tumour control. For further investigation, these two extracts were assessed for inhibitory effect neovascularisation induced by MTA1 protein in the corneal micro pocket of Wister rat. The result proved that both extracts can effectively inhibit the formation of new blood vessels induced by MTA1 protein (Rachaiyah *et al.*, 2019).

10. Neuropharmacological activity

Methanolic extract of *D. alata* tuber has anxiolytic-like properties and exhibit moderate antidepressant effect based on the standard behavioural test on mice models (Amin *et al.*, 2018). Significant antidepressant properties with decrease in locomotor activity is probably due to the inhibition of serotonin and noradrenaline level in mice. Anxiolytic behaviour was proposed to be reflected from high level of neophilia. Thus, further research on isolating bioactive compound and their exact mechanism of action that contribute to this neuropharmacological activity by this plant (Amin *et al.*, 2018) is recommended.

11. Gastroprotective and gastrointestinal function

D. alata resistant starches (RS) have gastroprotective effect on ethanol-induced gastric injury in mice. Compared to model group of mice with ethanol-induced gastric ulcer, all four types of *D. alata* RS-pre-treated mice show attenuated level of histopathological injury and ulcerative lesion index (Mao *et al.*, 2018). Resistant starches promote gastric motility and generate more short chain fatty acid (SCFA) which lower pH value in intestinal tract thus inhibit saprophytic bacterial growth while promote probiotics

population in the stomach. Significantly elevated SOD level with MDA level significantly reduced prove that *D. alata* RS has antioxidative effect *in vivo* and probably is one of the mechanisms associated in gastroprotective activity in ethanol-induced mice (Mao *et al.*, 2018). Based on Cheng-Chin Hsu *et al.* (2006), Chinese yam improved gastrointestinal function by inhibiting the population of *Clostridium perfringens* ($p < 0.05$) and promoted the growth of intestinal microflora (*Bifidobacterium* and *Lactobacillus*) in mice's small intestine. The mechanism was proposed as yam contains soluble fibre and resistant starch that effectively changed intestinal microflora variation. *D. alata* consumption also significantly increases intestinal enzymes activity of leucine aminopeptidase, lipase, sucrase and maltase ($p < 0.05$) in dose-dependent manner. The antioxidant activity exhibited from pre-intake of yam was proven based on significant decline of MDA activity and fibronectin level with increase in superoxide dismutase (SOD) activity compared to lipopolysaccharide (LPS)-treated control group without yam supplement. Therefore, it is assumed that dietary fibre, polyphenol and flavonoids might contribute to observed gastrointestinal functions and antioxidant protection exhibited. Similar study also reported an intake of 25% yam supplementation efficiently modulated intestinal enzyme activity. However, plasma and hepatic cholesterol level could only be decreased by 50% of yam supplementation with increased faecal steroid extractions. It is suggested that the decrease of fat, cholesterol and bile acid absorption was due to increased viscosity of the digesta and the thickness of unstirred layer in small intestine caused by yam mucilage (Chen *et al.*, 2003) which warrants further investigation.

12. Cardioprotective activity

Taiwanese and Japanese yam possess significant cardioprotective properties against doxorubicin (DOX)-induced damage via multiple effects on antioxidant, anti-inflammatory and antiapoptotic activities (Chen *et al.*, 2017). Ethanol extract of *D. alata* recovered the most cardiotoxicity effect from DOX treatment by improving cardiac physical and functional parameters on experimental mice. Preserved heart function correlates with reduction in oxidative stress level, inflammation status in cardiomyocytes

and significant decrease in apoptotic response. This finding is truly useful to combat the use of DOX as chemotherapeutic agent in cancer treatment as it has the potential to cope with major side effect of DOX which is cardiotoxicity. Inhibition of thiobarbituric acid reactive substance (TBARS) and ROS with concomitant decline in serum lactic acid dehydrogenase (LDH) while restoring GSH level, GPx and SOD activities in heart tissue show ethanol extract of *D. alata* exhibit antioxidant activity. Anti-inflammation could be observed from reduced protein level of mRNA and NF- κ B and cardiac level of pro-inflammation cytokines. Cotreatments with *D. alata* showed antiapoptosis activity from the dramatically decline of DOX-dependent cleavage caspase and PARP-1 expression as well as cytosolic cytochrome c release. However, the mechanism of caspase activation inhibition by the extract is yet to be understood. Diosgenin was suggested as the mediating candidate responsible for all activities exhibited (Chen *et al.*, 2017) but further work is needed to clarify the claim.

13. Other activities

Estrogenic compounds identified from ethyl acetate extract of *D. alata* could activate human estrogen receptor, ER α and ER β , providing evidence for further research on beneficial intake of yam among menopausal women. The study speculated that phenolic hydroxyl group (hydro-Q9 chromene, γ -tocopherol-9, RRR- α -tocopherol and coenzyme Q9) might play a role in the binding with the estrogen receptor besides being a good antioxidant (Cheng *et al.*, 2007).

Aqueous extract of *D. alata* was proposed to act as a novel fibrosis antagonist by suppressing β -HB-induced expression of fibronectin in NRK-49F cell along with inhibition of Smad2/3, pSmad2/3 and Smad4. This action provides nephroprotective effect of *D. alata* by down regulation of TGF- β signalling pathway and EMT expression based on *in vitro* test (Liu *et al.*, 2012).

Fermentation of *D. alata* causes significant increase in some mineral content such as calcium, magnesium, potassium and phosphorus. However, there was also antinutrient content determined by decrease of oxalate and tannin in fermented yam compared to raw one. The pH value reduced as the fermentation progressed with no

change in phytate content (Bello *et al.*, 2012). Therefore, this finding showed that fermented *D. alata* could be used as a functional food due to its elevated mineral content than raw yam.

IV. CONCLUSION

In summary, this review analysed the pharmacological activities of three *Dioscorea* spp. namely *D. alata*, *D. hispida* and *D. bulbifera* through scientific findings on several relevant clinical and preclinical studies. We could conclude that dioscorin, diosgenin, alkaloid, anthocyanin and myricetin from the flavonoid groups were the main compounds involved in the biological activities of these yams. The tuber or rhizome of the yam contains most of the bioactive compounds and carry various pharmacological activities. This article addressed the application of *Dioscorea* spp. as therapeutic medicine plant that possessed antioxidant, immunomodulatory, antiosteoporotic, antimicrobial, antihypertensive, nanoparticulate synthesis, gastroprotective, neuropharmacological, cardioprotective and nephroprotective effects. Various pharmacological activities have been demonstrated by these plants, although data on their mechanism of action are very limited. Therefore, further research needs to be conducted to determine the specific mechanism of action of the pharmacological activities in order to realise the full potential of these plants as future therapeutics.

V. ACKNOWLEDGEMENT

We would like to thank Universiti Teknologi MARA Puncak Alam Campus for the opportunity to finish this review. We also thank to Dr. Hussein Mohammad, Head of Toxicology and Pharmacology Unit, Herbal Medicine Research Centre, Institute for Medical Research, National Institute of Health, Setia Alam for assistance in completing this review.

VI. REFERENCES

- Adeosun, OM, Arotupin, DJ, Toba, OA & Adewole, A 2016, 'Antibacterial activities and phytochemical properties of extracts of *Dioscorea bulbifera* Linn (Air Potatoe) tubers and peels against some pathogenic bacteria'. vol. 5, no. 1, pp. 20–26.
- Agyare, C, Spiegler, V, Asase, A, Scholz, M, Hempel, G & Hensel, A 2018, 'An ethnopharmacological survey of medicinal plants traditionally used for cancer treatment in the Ashanti region, Ghana'. Journal of Ethnopharmacology, vol. 212, pp. 137–152.
- Ahmed, Z, Chishti, MZ, Johri, RK, Bhagat, A, Gupta, KK & Ram, G 2009, 'Antihyperglycemic and antidiabetic activity of aqueous extract of *Dioscorea bulbifera* tubers. *Diabetologia Croatica*', vol. 38, no. 3, pp. 63–72.
- Amin, KMR, Uddin, MG, Rashid, MMO & Sharmin, T 2018, 'New insight in neuropharmacological activities of *Dioscorea alata*', *Discovery Phytomedicine*, vol. 5, no.1, pp. 1–6.
- Aminah, NS, Yulvia, A & Tanjung, M 2017, 'Methyl-3,4-dihydroxybenzoate and 9-10-dihydrophenanthrene-2,4,7-triol two phenolic compounds from *Dioscorea alata* L. and their antioxidant activity'. AIP Conference Proceedings, p. 1888.
- Anisuzzman, M, Zilani, MNH, Khushi, SS, Asaduzzman, M & Hossain, MG 2016, 'Antioxidant, Antibacterial Potential and HPLC Analysis of *Dioscorea alata* Bulb', *Indonesian Journal of Pharmacy*, vol. 27, no. 1, pp. 9–14.
- Azman, I, Mutalib, SA, Yusoff, SFM, Fazry, S, Noordin, A, Kumaran, M & Mat Lazim, A 2016, 'Novel *Dioscorea hispida* starch-based hydrogels and their beneficial use as disinfectants'. *Journal of Bioactive and Compatible Polymers*, vol. 31, no. 1, pp. 42–59.
- Behera, KK, Sahoo, S & Prusti, A 2010, 'Biochemical Quantification of Diosgenin and Ascorbic Acid from the Tubers of Different *Dioscorea* Species Found in Orissa', *Libyan Agriculture Research Center Journal International*, vol. 2, no. 2, pp. 123–127.
- Bello, BK, Ojokoh, AO & Ojokoh, SE 2012, 'Mineral and antinutritional composition of fermented water yam (*Dioscorea alata*)', *International Journal of Life Sciences and Technology*, vol. 5, no. 3, pp. 20–23.
- Chang, SJ, Lee, YC, Liu, SY & Chang, TW 2004, 'Chinese Yam (*Dioscorea alata* cv. Tainung No. 2) Feeding Exhibited Antioxidative Effects in Hyperhomocysteinemia Rats', *Journal of Agricultural and Food Chemistry*, vol. 52, no. 6, pp. 1720–1725.
- Chatterjee, A, Das, A, Chaudhuri, D & Mandal, N 2012, 'Study of antioxidant and reactive oxygen species scavenging activity of the edible tuber of "greater yam" (*Dioscorea alata* L.) from North-East India', *Asian Journal of Pharmaceutical and Clinical Research*, vol. 5, no. 3, pp. 74–84.
- Chen, CT, Wang, ZH, Hsu, CC, Lin, HH & Chen, JH 2017, 'Taiwanese and Japanese yam (*Dioscorea* spp.) extracts attenuate doxorubicin-induced cardiotoxicity in mice', *Journal of Food and Drug Analysis*, vol. 25, no.4, pp. 872–880.
- Chen, HL, Wang, CH, Chang, CT & Wang, TC 2003, 'Effects of Taiwanese yam (*Dioscorea alata* L. cv. Tainung No. 2) on the mucosal hydrolase activities and lipid metabolism in Balb/c mice', *Nutrition Research*, vol. 23, no. 6, pp. 791–801.
- Cheng, WY, Kuo, YH & Huang, CJ 2007, 'Isolation and Identification of Novel Estrogenic Compounds in Yam Tuber (*Dioscorea alata* cv. Tainung No. 2)', *Journal of Agricultural and Food Chemistry*, vol. 55, no. 18, pp. 7350–7358.
- Chinko, BC, Dapper, DV & Adienbo, OM 2020, 'Evaluation of Antihyperlipidaemic Activities of Hydromethanolic Extracts of *Dioscorea bulbifera*', *Journal of Advances in Medical and Pharmaceutical Sciences*, vol. 22, no. 1, pp. 16–25.
- Chopade, BA, Ghosh, S, Ahire, M, Patil, S, Jabgunde, A, Bhat Dusane, M, Joshi, BN, Pardesi, K, Jachak, S & Dhavale, DD 2012, 'Antidiabetic activity of *Gnidia glauca* and *Dioscorea bulbifera*: Potent amylase and glucosidase inhibitors', *Evidence-Based Complementary and Alternative Medicine*, vol. 2012.
- Dahiya, P 2017, 'Phytochemical investigation and antimicrobial properties of *Dioscorea bulbifera* tuber', *Asian Journal of Pharmaceutical and Clinical Research*, vol. 10, no. 12, pp. 317–319.
- Daud Om, A, Azlan Azizan, K & Baharum, SN 2016, 'Phytochemical Screening of Ubi Gadong (*Dioscorea hispida*) by using GC-MS', in *Seminar dan konvensyen penyelidikan perikanan*, August.
- Dey, P & Chaudhuri, TK 2014, 'In vitro modulation of TH1 and TH2 cytokine expression by edible tuber of *Dioscorea*

- alata* and study of correlation patterns of the cytokine expression', *Food Science and Human Wellness*, vol. 3, no. 1, pp. 1–8.
- Dey, P, Chowdhuri, SR, Sarkar, MP & Chaudhuri, TK 2016, 'Evaluation of anti-inflammatory activity and standardisation of hydro-methanol extract of underground tuber of *Dioscorea alata*', *Pharmaceutical Biology*, vol. 54, no. 8, pp. 1474–1482.
- Dey, P, Ray, S & Chaudhuri, TK 2016, 'Immunomodulatory activities and phytochemical characterisation of the methanolic extract of *Dioscorea alata* aerial tuber', *Journal of Functional Foods*, vol. 23, pp. 315–328.
- Dsouza, MR, Hana, CD & Rufina, K 2019, 'Diosgenin from *Dioscorea Alata*: Extraction and Potential Effects on Enzymes Related to Metabolic Syndrome', *International Journal of Pharmacy and Biological Sciences*, vol. 9, no. 1, 177–185.
- Dufie, WMF, Oduro, I, Ellis, WO, Asiedu, R & Maziya-Dixon, B 2013, 'Potential health benefits of water yam (*Dioscorea alata*)', *Food & Function*, vol. 4, no. 10, pp. 1496–1501.
- Enweani, IB 2017, 'Comparative Study of The Phytochemical and Antibacterial Comparative Study of The Phytochemical and Antibacterial Properties of Two Different Varieties of *Dioscorea bulbifera* Tubers', January 2016.
- Estiasih, T, Umara, D & Harijono, H 2018, 'Hypoglycemic effect of crude water soluble polysaccharide extracted from tubers of purple and yellow water yam (*Dioscorea alata* L.) on alloxan-induced hyperglycemia Wistar rats', *Progress in Nutrition*, vol. 20, no. 5, pp. 59–67.
- Fu, SL, Hsu, YH, Lee, PY, Hou, WC, Hung, LC, Lin, CH, Chen, CM & Huang, YJ 2006, 'Dioscorin isolated from *Dioscorea alata* activates TLR4-signaling pathways and induces cytokine expression in macrophages', *Biochemical and Biophysical Research Communications*, vol. 339, no. 1, pp.137–144.
- Gao, H, Kuroyanagi, M, Wu, L, Kawahara, N, Yasuno, T & Nakamura, Y 2002, 'Antitumor-promoting constituents from *Dioscorea bulbifera* L. in JB6 mouse epidermal cells', *Biological and Pharmaceutical Bulletin*, vol. 25, no. 9, pp. 1241–1243.
- Ghosh, S, Jagtap, S, More, P, Shete, UJ, Maheshwari, NO, Rao, SJ, Kitture, R, Kale, S, Bellare, J, Patil, S, Pal, JK & Chopade, BA 2015, '*Dioscorea bulbifera* mediated synthesis of novel Au-core-Ag-shell nanoparticles with potent antibiofilm and antileishmanial activity', *Journal of Nanomaterials*, vol. 2015.
- Ghosh, S, More, P, Derle, A, Kitture, R, Kale, T, Gorain, M, Avasthi, A, Markad, P, Kundu, GC, Kale, S, Dhavale, DD, Bellare, J & Chopade, BA 2015, 'Diosgenin functionalized iron oxide nanoparticles as novel nanomaterial against breast cancer', *Journal of Nanoscience and Nanotechnology*, vol. 15, no. 12, pp. 9464–9472.
- Ghosh, S, More, P, Derle, A, Patil, AB, Markad, P, Asok, A, Kumbhar, N, Shaikh, ML, Ramanamurthy, B, Shinde, VS, Dhavale, DD & Chopade, BA 2014, 'Diosgenin from *Dioscorea bulbifera*: Novel hit for treatment of type II diabetes mellitus with inhibitory activity against α -amylase and α -glucosidase', *PLoS ONE*, vol. 9, no. 9.
- Ghosh, S, Patil, S, Ahire, M, Kitture, R, Kale, S, Pardesi, K, Cameotra, S, Bellare, J, Dhavale, DD, Jabgunde, A & Chopade, BA 2012, 'Synthesis of silver nanoparticles using *Dioscorea bulbifera* tuber extract and evaluation of its synergistic potential in combination with antimicrobial agents', *International Journal of Nanomedicine*, vol. 7, pp. 483–496.
- Guo, X, Sha, X, Cai, S, Wang, O & Ji, B 2015, 'Antiglycative and Antioxidative Properties of Ethyl Acetate Fraction of Chinese Purple Yam (*Dioscorea alata* L.) Extracts', *Food Science and Technology Research*, vol. 21, no. 4, pp. 563–571.
- Guo, X, Sha, X, Liu, J, Cai, S, Wang, Y & Ji, B 2015, 'Chinese Purple Yam (*Dioscorea alata* L.) Extracts Inhibit Diabetes-Related Enzymes and Protect HepG2 Cells Against Oxidative Stress and Insulin Resistance Induced by FFA', *Food Science and Technology Research*, vol. 21, no. 5, pp. 677–683.
- Han, CH, Lin, YF, Lin, YS, Lee, TL, Huang, WJ, Lin, SY & Hou, WC 2014, 'Effects of yam tuber protein, dioscorin, on attenuating oxidative status and learning dysfunction in d-galactose-induced BALB/c mice', *Food and Chemical Toxicology*, vol. 65, pp. 356–363.
- Han, CH, Liu, JC, Fang, SU & Hou, WC 2013, 'Antioxidant activities of the synthesized thiol-contained peptides derived from computer-aided pepsin hydrolysis of yam tuber storage protein, dioscorin', *Food Chemistry*, vol. 138, no. 2–3, pp. 923–930.
- Han, CH, Lin, YF, Lin, YS, Lee, TL, Huang, WJ, Lin, SY & Hou, WC 2014, 'Effects of yam tuber protein, dioscorin, on attenuating oxidative status and learning dysfunction in d-galactose-induced BALB/c mice', *Food and Chemical Toxicology*, vol. 65, pp. 356–363.
- Harijono, Estiasih, T, Sunarharum, WB & Hartono, MD

- 2013, 'Hypoglycemic effect of biscuits containing water-soluble polysaccharides from wild yam (*Dioscorea hispida* Dennst) or lesser yam (*Dioscorea esculenta*) tubers and alginate', *International Food Research Journal*, vol. 20, no. 5, pp. 2279–2285.
- Hazrin-Chong, NH, Azeem, AM, Mat Zin, NNIN & Mat Lazim, MAS 2018, 'Effectiveness of *Dioscorea hispida* Dennst as antibacterial and antibiofilm agent', *Malaysian Journal of Microbiology*, vol. 14, no. (Special Issue 6), pp. 462–467.
- Hsu, CK, Yeh, JY & Wei, JH 2011, 'Protective effects of the crude extracts from yam (*Dioscorea alata*) peel on tert-butylhydroperoxide-induced oxidative stress in mouse liver cells', *Food Chemistry*, vol. 126, no. 2, pp. 429–434.
- Hsu, Chao-Chin, Kuo, HC & Huang, KE 2017, 'The Effects of Phytosterols Extracted from *Dioscorea alata* on the Antioxidant Activity, Plasma Lipids, and Hematological Profiles in Taiwanese Menopausal Women', *Nutrients*, vol. 9, no. 12, p. 1320.
- Hsu, Cheng-Chin, Huang, YC, Yin, MC & Lin, SJ 2006, 'Effect of Yam (*Dioscorea alata* Compared to *Dioscorea japonica*) on Gastrointestinal Function and Antioxidant Activity in Mice', *Journal of Food Science*, vol. 71, no. 7, pp. S513–S516.
- Hsu, FL, Lin, YH, Lee, MH, Lin, CL & Hou, WC 2002, 'Both Dioscorin, the Tuber Storage Protein of Yam (*Dioscorea alata* cv. Tainong No. 1), and Its Peptic Hydrolysates Exhibited Angiotensin Converting Enzyme Inhibitory Activities', *Journal of Agricultural and Food Chemistry*, vol. 50, no. 21, pp. 6109–6113.
- Hsu, YJ, Hsu, JH & Lin, KC 2015, 'Yam storage protein dioscorins modulate cytokine gene expression in BALB/c and C57BL/6 lymphocytes', *Food and Agricultural Immunology*, vol. 26, no. 6, pp. 909–923.
- Igbokwe, CJ, Akubor, PI & Mbaeyi-nwaoha, IE 2017, 'Effect of Steam Blanching and Sulphiting on the Antidiabetic Potentials of Aerial Yam (*D. bulbifera*) Amala Flour Fed Alloxan Induced Diabetic Rats', *Food Science and Technology*, vol. 5, no. 3, pp 80–85.
- Jose, A, Nizar, S, Vishnu MR & M. Anil, K 2019, 'Antioxidant Potential in Relation to Total Phenolics and Pigment Contents Among the Selected Landraces of *Dioscorea alata* L. in Kerala, India', *Journal of Experimental Biology and Agricultural Sciences*, vol. 7, no. 4, pp. 403–410.
- Jumari, Soeprbowati, TR & Nafisa, AR 2019, 'Alternatif Main Food from *Dioscorea alata*: Its Potency from Central Java, Indonesia', *Journal of Physics: Conference Series*, vol. 1217, no. 1, p. 012172.
- Kamaruddin, ZH, Sapuan, SM, Mohamed Yusoff, MZ & Jumaidin, R 2020, 'Rapid detection and identification of dioscorine compounds in *Dioscorea hispida* tuber plants by LC-ESI-MS', *BioResources*, vol. 15, no. 3, pp. 5999–6011.
- Kartini, N, Ramli, M & Nur, K 2018, 'Potential Antifungal Activity of *Dioscorea daemona* (Ubi Gadong) Tuber Extract Against *Pyricularia grisea* Pathogen of Rice Blast Disease', vol. 1, no. 01, pp 47–55.
- Kaur, C & Kapoor, HC 2002, 'Anti-oxidant activity and total phenolic content of some Asian vegetables', *International Journal of Food Science and Technology*, vol. 37, no. 2, pp. 153–161.
- Kresnadipayana, D & Waty, HI 2019, 'Concentration of NaCl soaking to decreasing cyanide levels in Gadung (*Dioscorea hispida* Dennst)', *Jurnal Teknologi Laboratorium*, vol. 8, no. 1, pp. 36–40.
- Kuete, V, Bertrand Teponno, R, Mbaveng, AT, Tapondjou, LA, Meyer, JJM, Barboni, L & Lall, N 2012, 'Antibacterial activities of the extracts, fractions and compounds from *Dioscorea bulbifera*', *BMC Complementary and Alternative Medicine*, vol. 12, pp. 3–10.
- Lin, D, Guo, X, Gao, H, Cheng, L, Cheng, M, Song, S, Peng, Y & Zheng, J 2015, 'In Vitro and in Vivo Studies of the Metabolic Activation of 8-Epidiosbulbin e Acetate', *Chemical Research in Toxicology*, vol. 28, no. 9, pp. 1737–1746.
- Lin, JY, Lu, S, Liou, YL & Liou, HL 2006, 'Increased IgA and IgG serum levels using a novel yam–boxthorn noodle in a BALB/c mouse model', *Food and Chemical Toxicology*, vol. 44, no. 2, pp. 170–178.
- Lin, PL, Lin, KW, Weng, CF & Lin, KC 2009, 'Yam Storage Protein Dioscorins from *Dioscorea alata* and *Dioscorea japonica* Exhibit Distinct Immunomodulatory Activities in Mice', *Journal of Agricultural and Food Chemistry*, vol. 57, no. 11, pp. 4606–4613.
- Liu, SF, Chang, SY, Lee, TC, Chuang, LY, Guh, JY, Hung, CY, Hung, TJ, Hung, YJ, Chen, PY, Hsieh, PF & Yang, YL 2012, '*Dioscorea alata* Attenuates Renal Interstitial Cellular Fibrosis by Regulating Smad- and Epithelial-Mesenchymal Transition Signaling Pathways', *PLoS ONE*, vol. 7, no. 11, pp. 1–8.
- Liu, YH, Lin, YS, Liu, DZ, Han, CH, Chen, CT, Fan, M & Hou, WC 2009, 'Effects of different types of yam (*Dioscorea alata*) products on the blood pressure of spontaneously hypertensive rats', *Bioscience*,

- Biotechnology, and Biochemistry, vol. 73, no. 6, pp. 1371–1376.
- Liu, YW, Liu, JC, Huang, CY, Wang, CK, Shang, HF & Hou, WC 2009, 'Effects of Oral Administration of Yam Tuber Storage Protein, Dioscorin, to BALB/c Mice for 21-Days on Immune Responses', *Journal of Agricultural and Food Chemistry*, vol. 57, no. 19, pp. 9274–9279.
- Lokman, EF, Muhammad, H, Awang, N, Hasyima Omar, M, Mansor, F & Saparuddin, F 2017, 'Gene Expression Profiling associated with Hepatotoxicity in Pregnant Rats treated with Ubi Gadong (*Dioscorea hispida*) Extract', *International Journal of Biomedical Science: IJBS*, vol. 13, no. 1, pp. 26–34.
- Lu, YL, Chia, CY, Liu, YW & Hou, WC 2012, 'Biological activities and applications of dioscorins, the major tuber storage proteins of yam', *Journal of Traditional and Complementary Medicine*, vol. 2, no. 1, pp. 41–46.
- Mahmad, N, Taha, RM, Othman, R, Abdullah, S, Anuar, N, Elias, H & Rawi, N 2018, 'Anthocyanin as potential source for antimicrobial activity in *Clitoria ternatea* L. and *Dioscorea alata* L', *Pigment & Resin Technology*, vol. 47, no. 6, pp. 490–495.
- Maithili, V, Dhanabal, S, Mahendran, S & Vadivelan, R 2011, 'Antidiabetic activity of ethanolic extract of tubers of *Dioscorea alata* in alloxan induced diabetic rats', *Indian Journal of Pharmacology*, vol. 43, no. 4, pp. 455–459.
- Makiyah, SNN, Noor, Z, Widodo, N, Rifa'i, M & Djati, MS 2014, 'Ethanol Extracts of Tubers *Dioscorea alata* L. as Antiallergic', *International Journal of Pharma and Bio Sciences*, vol. 5, no. 3, pp. 214–220.
- Mao, X, Lu, J, Huang, H, Gao, X, Zheng, H, Chen, Y, Li, X & Gao, W 2018, 'Four types of winged yam (*Dioscorea alata* L.) resistant starches and their effects on ethanol-induced gastric injury in vivo', *Food Hydrocolloids*, vol. 85, pp. 21–29.
- Masdar, ND, Roslan, RAB, Hasan, S & Kamal, ML 2020, 'Determination of Antioxidant from Ubi Gadong Tubers for Facial Soap Bar', *Charting the Sustainable Future of ASEAN in Science and Technology*, pp. 193–201.
- Miah, MM, Das, P, Ibrahim, Y, Shajib, MS & Rashid, MA 2018, 'In vitro antioxidant, antimicrobial, membrane stabilization and thrombolytic activities of *Dioscorea hispida* Dennst', *European Journal of Integrative Medicine*, vol. 19, pp. 121–127.
- Moriya, C, Hosoya, T, Agawa, S, Sugiyama, Y, Kozono, I, Shin-ya, K, Terahara, N & Kumazawa, S 2015, 'New acylated anthocyanins from purple yam and their antioxidant activity', *Bioscience, Biotechnology, and Biochemistry*, vol. 79, no. 9, pp. 1484–1492.
- Murthy, GP, Chandrasekhar, KB, Ravishankar, DK, Leelaja, BC, Lokesh, S & Manju, B 2017, 'Evaluation of Validated Herbal Medicine Formulation for Antiproliferative and Apoptotic Activities Used in the Tribal Medicine System', *IOSR Journal of Applied Chemistry*, vol. 10, no. 1, pp. 05–24.
- Napisah, H, Azmahani, A, Intan, A & Nazifah, A 2011, 'A Preliminary Study on the Antimicrobial Properties of Several Plants Collected from Terengganu, Malaysia', *Journal of Agrobiotechnology*, vol. 2, no. 0, pp. 99–106.
- Narkhede, A, Gill, J, Thakur, K, Singh, D, Singh, E, Kulkarni, O, Harsulkar, A & Jagtap, S 2013, 'Total polyphenolic content and free radical quenching potential of *Dioscorea alata* L. tubers', *International Journal of Pharmacy and Pharmaceutical Sciences*, vol. 5, no. 3, pp. 866–869.
- Nudin, NFH, Ali, AM, Ngah, N, Mazlan, NZ, Mat, N, Ghani, MNA, Alias, N, Zakaria, AJ & Jahan, MS 2017, 'ISSR marker-assisted genetic diversity analysis of *Dioscorea hispida* and selection of the best variety for sustainable production', *Comptes Rendus - Biologies*, vol. 340, no. 8, pp. 359–366.
- Nugroho, LH & Estyaniana, A 2018, 'The potency of gadung (*Dioscorea hispida* Dennst.) tuber as a functional food: Toxicity, phytochemical content and starch characters', *AIP Conference Proceedings*, vol. 2002, no. 2018.
- Nur, RM & Nugroho, LH 2018, 'Cytotoxic activities of fractions from *Dioscorea bulbifera* L. Chloroform and methanol extracts on T47D breast cancer cells', *Pharmacognosy Journal*, vol. 10, no. 1, pp. 33–38.
- Osukoya, OA & Kuku, A 2020, 'Physicochemical, enzymatic and molecular characterisation of the storage protein of aerial tuber, *Dioscorea bulbifera* Linn', *Journal of Genetic Engineering and Biotechnology*, vol. 18, no. 1.
- Panduranga Murthy, G, Chandrasekhar, KB, Leelaja, BC & Lokesh, S 2015, 'Antimicrobial and Antioxidant Activities of Tribal Medicine Formulation (TMF) accomplished for Wound related remedies in Biligirirangana Hill area of Chamarajanagara district, Karnataka (India)', *International Journal of Pharmaceutical Chemistry*, vol. 5, no. 4, pp. 104–114.
- Panduranga Murthy, G, Punith Kumar, TG, Suresh, A, Raviashankar, HG, Chandrasekhar, KB & Lokesh, S 2011, 'Evaluation of ethanolic leaf extract of *Dioscorea hispida* Dennst. for anti-inflammatory and analgesic activities', *Int*

- J. Pharm & Ind. Res, vol. 1, no. 2, pp. 83–87.
- Peng, KY, Horng, LY, Sung, HC, Huang, HC & Wu, RT 2011, 'Antiosteoporotic Activity of *Dioscorea alata* L. cv. Phyto through Driving Mesenchymal Stem Cells Differentiation for Bone Formation', Evidence-Based Complementary and Alternative Medicine, vol. 2011, pp. 1–12.
- Pugazhendhi, S, Sathya, P, Palanisamy, PK & Gopalakrishnan, R 2016, 'Synthesis of silver nanoparticles through green approach using *Dioscorea alata* and their characterization on antibacterial activities and optical limiting behavior', Journal of Photochemistry & Photobiology B: Biology, vol. 159, pp. 155–160.
- Rachaiyah, K, Keshavan, D, & Salimath, BP 2019, 'Anti-Neoplastic Activity of *Dioscorea Bulbifera* Root Extracts by Targeting Mta1', vol. 5, no. 549, pp. 549–563.
- Ghosh, S, Nitnavare, R, Dewle, A, Tomar, GB, Chippatti, T, R, More, P, Kitture, R, Kale, S, Belle, J & Choppade, BA 2015, 'Novel platinum–palladium bimetallic nanoparticles synthesized by *Dioscorea bulbifera*: Anticancer and antioxidant activities', International Journal of Nanomedicine, vol. 10, pp. 7477–7490.
- Saklani, S, Garhwal, S, Kothiyal, SC & Garhwal, S 2013, 'Nutritional Profile, Antinutritional Profile and Phytochemical Screening of Garhwal Himalaya Medicinal Plant *Dioscorea alata* Tuber', International Journal of Pharmaceutical Sciences Review and Research, vol. 23, no. 2, pp. 42–46.
- Sakthidevi, G & Mohan, VR 2013, 'Total phenolic, flavonoid contents and in vitro antioxidant activity of *Dioscorea alata* L. tuber', Journal of Pharmaceutical Sciences and Research, vol. 55, pp. 115–119.
- Saleha, S, Saidi, NSM, Rasnovi, S & Iqbalsyah, TM 2018, 'Nutritional Composition of *Dioscorea hispida* from Different Locations Around Leuser Ecosystem Area', Jurnal Natural, vol. 18, no.1, pp. 1–6.
- Santos-Sánchez, F, Salas, CR, Claudia Villanueva, C & Hernández, CB 2019, 'Antioxidant Compounds and Their Antioxidant Mechanism', Intech Open.
- Sasiwatpaisit, N, Thitikornpong, W, Palanuvej, C & Ruangrungsi, N 2014, 'Dioscorine content in *Dioscorea hispida* dried tubers in Thailand by TLC-densitometry and TLC image analysis', Journal of Chemical and Pharmaceutical Research, vol. 6, no. 4, pp. 803–806.
- Sharma, S, Gupta, R, & Deswal, R 2017, '*Dioscorea alata* tuber proteome analysis shows over thirty dioscorin isoforms and novel tuber proteins', Plant Physiology and Biochemistry, vol. 114, pp. 128–137.
- Sheikh, N, Kumar, Y, Misra, AK & Pfoze, L 2013, 'Phytochemical screening to validate the ethnobotanical importance of root tubers of *Dioscorea* species of Meghalaya, North East India', Journal of Medicinal Plants Studies Year, vol. 1, no. 6.
- Tamaroh, S, Raharjo, S, Murdiati, A & Anggrahini, S 2018, 'Total Phenolic Content and Antioxidant Activity of Anthocyanin Extract from Purple Yam (*Dioscorea alata* L.) Flour Using Different Solvents', Pakistan Journal of Nutrition, vol. 17, no. 6, pp. 260–267.
- Tsai, HL, Yan, JL, Wang, SM, & Chang, SJ 2009, 'Neuroprotection against hyperhomocysteinemia-induced selective oxidative stress in brain regions of rats with folic acid or *Dioscorea alata* supplementation', Current Topics in Nutraceutical Research, vol. 7, no. 2, pp. 73–80.
- Viji, MO, Neeba, W & Veena, VV 2016, 'Phytochemical Profiling of Tuber Extracts of *Dioscorea alata*', VISTAS, vol. 5, no. 1, pp. 133–137.
- Wang, TS, Lii, CK, Huang, YC, Chang, JY & Yang, FY 2011, 'Anticlastogenic effect of aqueous extract from water yam (*Dioscorea alata* L.)', Journal of Medicinal Plants Research, vol. 5, no. 26, pp. 6192–6202.
- Wei, Y, Xu, Y, Han, X, Qi, Y, Xu, L., Xu, Y, Yin, L, Sun, H, Liu, K & Peng, J 2013, 'Anti-cancer effects of dioscin on three kinds of human lung cancer cell lines through inducing DNA damage and activating mitochondrial signal pathway', Food and Chemical Toxicology, vol. 59, pp. 118–128.
- Wu, ZT, Li, ZQ, Shi, W, Wang, LL, Jiang, Y, Li, P & LI, H. 2020 'The crucial role of metabolic regulation in differential hepatotoxicity induced by furanoids in *Dioscorea bulbifera*', Chinese Journal of Natural Medicines, vol. 18, no. 1, pp. 57–69.
- Zhang, J, Tian, H, Zhan, P, Du, F, Zong, A & Xu, T 2018, 'Isolation and identification of phenolic compounds in Chinese purple yam and evaluation of antioxidant activity', LWT - Food Science and Technology, vol. 96, pp. 161–165.