Chapter 12
Dioscorea opposite Thunb. 山药 (Shanyao, Chinese Yam)

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12.1 Botanical Identity

Yam (*Dioscorea* species), a member of the monocotyledonous family *Dioscoreaceae*, is a nutritious food in West Africa, Southeast Asia, and the Caribbean. Yam has a deciduous perennial vine climbing to twenty feet with heart-shaped leaves and tiny green flowers. The tuberous rhizome of yam is pale brown, cylindrical, and twisted. There are over 600 species of *Dioscorea* in the world, about 40–50 of which are edible and widely used as medicinal food. Among them, Chinese yam (*D. opposite* Thunb.) (Fig. 12.1), mainly cultivated in Korea, Japan, and China [1, 2], is included in the Pharmacopoeia of the People's Republic of China [3] and is reported containin gallantoin, diosgenin, dioscine, gibberellins, dopamine, ergosterol, and mucilage [2, 4, 5]. It is widely used in traditional medicine for the treatment of anorexia, chronic diarrhea, asthma, dry coughs, oligunia, diabetes, seminal emission and excessive leucorrhea [3]. In Taiwan, 14 species, including *D. alata*, *D. alata* L. var. *purpurea*, *D. batatas*, *D. benthamii*, *D. bulbifera*, *D. collettii*, *D. cumingii*, *D. doryophora*, *D. esculenta*, *D. formosana*, *D. hispida*, *D. japonica*, *D. japonica* Thunb. var. *pseudojaponica*, and *D. japonica* Thunb. var. *oldhamii* are cultivated and consumed as a food with tonic functions. *D. alata* cv. Tainung No. 2 released by the Taiwan Agricultural Research Institute (TARI) for commercial production in 1996 is one of

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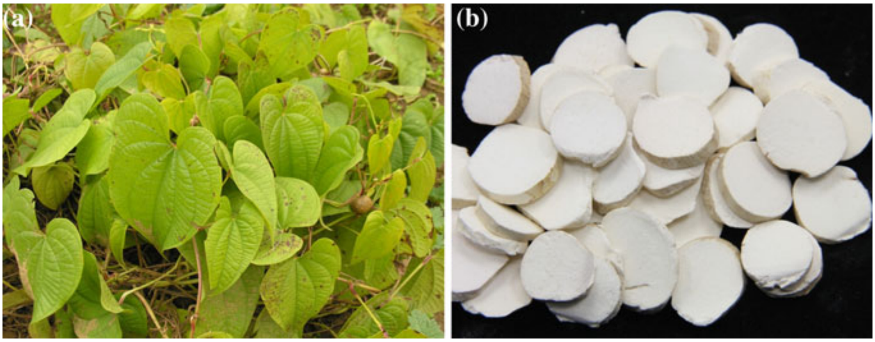


Fig. 12.1 Areal part of Chinese yam (*Dioscorea opposite*) with bulbils in leaf axil (**a**) and sliced dry roots as crude drug (**b**)

the most popular and widely cultivated yams in Taiwan due to its superior characteristics such as high nutritional values, resistance against anthracnose, high and stable productivity, and wide adaptability [6].

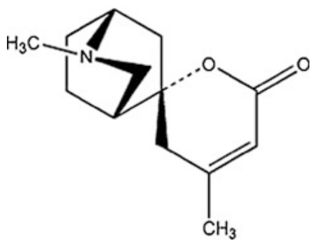
12.2 Chemical Constituents

The medicinal use of yam is mainly its tuber which contains two major classes of bioactive compounds, dioscorin and saponin (diosgenin and dioscin).

12.2.1 Dioscorin

Dioscorin (Fig. 12.2), the major storage protein of yam tuber, was successfully purified by using ammonium sulfate fractionation, DE-52 ion exchange chromatography, and Sephadex G-75 column from *D. batatas* Decne [7]. Two protein bands (82 and 28 kDa) were found under nonreducing conditions after SDS-PAGE; but only one band (32 kDa) was detected under reducing conditions. The purified dioscorin showed both CA (carbonic anhydrase) dehydration activity using sodium

Fig. 12.2 Chemical structure of dioscorin



bicarbonate as a substrate and CA activity staining after SDS-PAGE [7]. Dioscorin from *D. alata* L., purified and identified by ion-exchange chromatography, gel chromatography, SDS-PAGE, and MALDI-TOF-MS was made up of both dioscorin A (M.W. ~33 kDa) and dioscorin B (M.W. ~31 kDa) [8].

12.2.2 Diosgenin and Dioscin

Diosgenin and dioscin (aglyconediosgenin) are two major steroidal saponins in yams (Fig. 12.3). Teng et al. [9] found that diosgenin existed in both tubers and burbils of *D. opposite* in an amount of 0.0164 and 0.0213 %, respectively. Diosgenin is structurally similar to cholesterol. After oral administration, it is metabolized in the liver and eliminated via the bile [10]. Estrogenic and

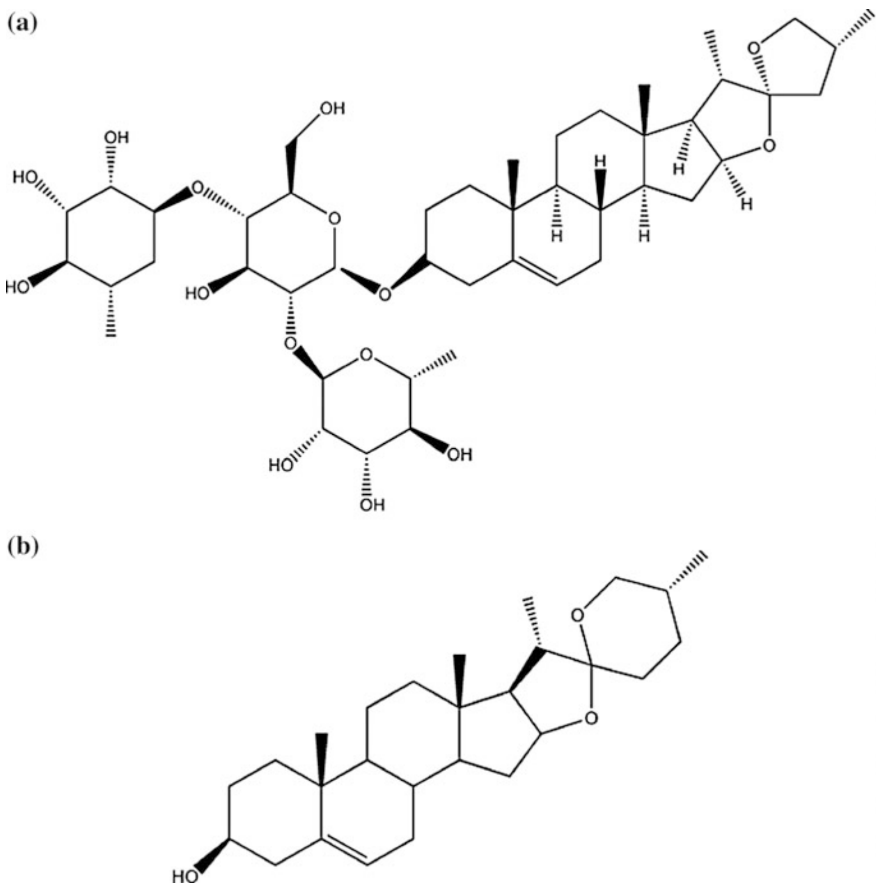


Fig. 12.3 Chemical structures of dioscin (**a**) and diosgenin (**b**)

anti-inflammatory effects of diosgenin have been hypothesized due to its structural similarity to estrogen precursors. Diosgenin has long been used as a raw material for the industrial production of steroid drugs [11] to suppress cholesterol absorption, increase cholesterol secretion through biliary excretion [12] and induce differentiation of the human erythroleukemia cell line by changing lipoxygenase activities [13]. It is also found to induce apoptosis and cell cycle arrest in a human osteosarcoma cell line [14] and exhibit prebiotic effect [15].

12.3 Pharmacological Studies

The medicinal use of yam is its tuber containing saponins, including dioscin or diosgenin, as well as alkaloids such as dioscorin, which are used as precursors for the manufacture of cortisone, estrogen, and progesterone-like compounds. Diosgenin exhibits estrogen-like functions in most people after ingesting yams, although human body lacks the enzymes to convert diosgenin into estrogen or any other steroid. Dioscorin and diosgenin with anti-inflammatory and muscle relaxant properties is beneficial for the arthritis and rheumatism. Moreover, yam tubers containing compounds that lower high blood cholesterol and reduce the risk of gallstone formation.

12.3.1 Hyperhomocysteinemia (HHcy)

In our laboratory, we found that freeze-dried yam (*D. alata*) feeding significantly alleviated hyperhomocysteinemia (HHcy) induced by methionine (Met) in rats. Thrombin-induced platelet aggregation (PA), plasma malondialdehyde levels (indicator of lipid peroxidation) and hepatic reactive oxygen species (indicator of oxidative stress) of HHcy rats were significantly lowered. Hepatic antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GRx) and glutathione reductase (GR) adaptively enhanced by Met feeding were unchanged by yam feeding. The beneficial effects of yam on HHcy are attributed to its antioxidant functions in alleviating PA, lipid peroxidation, and oxidative stress which is not due to the induction of antioxidant enzymes that have already been adaptively increased by HHcy [16].

12.3.2 Hyperlipidemia

Autolysate and enzymatic hydrolysates from *D. opposite* Thunb. tubers revealed extremely high antioxidant activities and high angiotensin I-converting enzyme (ACE) inhibitory activities, suggesting that yam tubers are an excellent source of antioxidant compounds with great antihypertensive activity [17]. The starch separated from the tuber of *D. opposite* cv. Anguo significantly decreased the serum total cholesterol (TC), triglyceride (TG) and LDL-cholesterol (LDL-C) levels by approximately 33.8, 46.2, and 27.5 %, respectively in hyperlipidemia rats, showing that starch from Chinese yam lowers blood lipid levels [18]. In our lab, three species of *D. alata* (TA01, TA03, and TA05) of Taiwan-cultivated yam (*Dioscorea*) were studied to examine the antioxidant and hypolipidemic functions in animal model. TA01 and TA03 were found to exhibit beneficial effects on lipid profile (TC, TG and LDL-C), fatty liver (TC) and antioxidant status (catalase and GR) for hyperlipidemia induced by a high fat and high cholesterol diet. Among these species, TA03 revealed the best efficacy in both hypolipidemic and antioxidant effects. With its function in regulating lipid profile and oxidative status, TA03 has the potential to be developed as a functional food for the prevention of cardiovascular disease [19]. Chen et al. found that a Taiwanese yam, *D. japonica* Thunb var. *pseudojaponica* Yamamoto, decreased gastric villous width. Diets consisting 25 and 50 % yams increased brush-border leucine aminopeptidase activity and decreased sucrase activity. The 50 % yam diet consistently improved the cholesterol profile in plasma and the liver, whereas the 25 % yam diet decreased the level of LDL-C cholesterol in plasma. Changes in blood lipid levels were associated with reduced fat absorption. This study suggests that a 25 % uncooked yam diet may benefit the function of upper gut and prevent hypercholesterolemia in humans, but the 50 % yam diet negatively affects protein absorption [20].

12.3.3 Hypoglycemic Effect

Diabetes mellitus is characterized by elevated plasma glucose levels resulting from absolute or relative insulin deficiency. The rhizomes of *D. opposite* Thunb. were traditionally used in diets to control Xiaokezheng (diabetes) in China. Certain reports confirmed that the water decoction of *D. opposite* has an anti-hyperglycemic effect to experimental diabetic mice [21]. Chemical components of *D. opposite,* dioscin and diosgenin, may be responsible for its medicinal efficacy [22, 23]. The anti-diabetic effects of *D. opposite* on dexamethasone-induced insulin resistance in vitro and in vivo found that *D. opposite* extract significantly decreased the blood insulin and glucose levels in dexamethasone-induced diabetic rats. *D. opposite* extract significantly enhanced insulin-stimulated glucose uptake in 3T3-L1 adipocytes in vitro. *D. opposite* extract also increased the mRNA expression of GLUT4 glucose transporter in 3T3-L1 adipocytes, suggesting that *D. opposite* restored insulin sensitivity via the regulation of GLUT4 expression [24]. McAnuff et al. [25] found that diabetic male Wistar rats fed with sapogenin extract from bitter yam (*D. polygonoides*) altered glucose metabolism with reduction in plasma glucose concentration. The Na^+-K^+-ATPase activity in the intestine was significantly reduced, which accounts for their hypoglycemic properties [26]. Supplementation of sapogenin extract from bitter yam (*D. polygonoides*) resulted in a significant decrease in lactase and maltase activities in the intestine of diabetic rats, indicating the bitter yam sapogenin extract exhibits hypoglycemic properties [27].

12.3.4 Reno- and Hepato-Protective Effects

Endemic liver disease has been one of the ten leading causes of death in Taiwan for many years [28]. Liver cirrhosis, caused by alcoholism, is a public health impact in Taiwan. Lee et al. evaluated the protective effects of the aqueous extract of the yam (*D. alata* L.) on acute kidney dysfunction by BUN (blood urea nitrogen) and creatinine, as well as on liver injuries by sGOT, sGPT and s-rGT in rats induced by ethanol. The pharmacological, biochemical, and pathological results indicated the decreased damage in renal tubules as well as decreased inflammation in the central vein and necrosis in the liver of rats treated with the extract of Chinese yam [29]. Crude water extract of yam (*D. alata* L.) revealed kidney secureness and liver fortification in rats with hepato-nephro-toxicity induced by acetaminophen (APAP). The pathologic sections exhibited improvements in renal tubular degranulation changes, necrosis, and disintegration. Protection against the inflammation of the central vein and necrosis of liver tissue was also reported. These results suggest that the yam protects the liver and kidneys against damage to preserve their functions [30]. Daily administration of yam significantly reduced the area of r-glutamino-transpeptidase (GGT)-positive foci and the proliferating cell nuclear index. The antioxidant activities of liver were also elevated in CCl_4-induced hepatic fibrosis of rats at a dose-dependent manner, suggesting that yam attenuates CCl_4-induced liver injury [31].

12.3.5 Improvement of Gastrointestinal Function

The Chinese yam, *D. opposite* Thunb., has been used to improve gastrointestinal function and cure diarrhea in traditional Chinese medicine (TCM) for many years [32]. Starch, a major polysaccharide, is the most abundant carbohydrate found in Chinese yam (20–60 %) [33]. Studies reported that Chinese Yam polysaccharides (CYPs) enhanced beneficial gut microbiota, but suppressed bacterial pathogens. Diversity of gut microflora was increased in CYP-supplemented rats compared to that in non-supplemented. CYP enriched beneficial gut microbiota, but suppressed bacterial pathogens in rat cecum, indicating that CYP is a good source of carbon and energy, and may improve bacterial community diversity and modulate short-chain fatty acid production in hindgut of rats [34]. Ingestion of 40 % ethanol extract of Chinese yam flour (*D. rhizoma*) suppressed the secretion of gastric acid and increased gastrointestinal motility and fecal quantity in Sprague-Dawley (SD) rats. The Chinese yam extract did not affect the growth of normal intestinal bacteria. However, a great deal of lactose-fermenting bacteria was observed in the fecal samples of rats fed with 2 % Chinese yam extract for 6 weeks. This finding would appear to suggest that Chinese yam extract not only induces an improvement in digestive capability, but also affects the conversion of some intestinal flora to probiotics. The serochemical analyses indicated that serum glucose, neutral lipid, and total cholesterol levels were reduced to certain degree by long-term feeding Chinese yam extract. This finding bolsters the notion that Chinese yam extract may be a useful alternative for patients suffering from hyperglycemia or hyperlipidemia [35].

12.3.6 Radio Protective Effect

Wang et al. using four lyophilized extracts obtained from yam rhizomes aqueous extract (YAE); 30 % ethanolic extract (YEE); aqueous extract boiled for 30 min (BYAE); and 30 % ethanolic extract boiled for 30 min (BYEE) to evaluate the protective effect on calf thymus DNA and plasmid DNA strand breakage. They found that YAE, YEE, and BYEE effectively inhibited the copper-driven Fenton reaction-induced damage of DNA, and the X-ray—induced strand breakage of plasmid DNA to a small extent. BYAE potently inhibited X-ray—induced strand breakage in plasmid pGL3 DNA but failed to inhibit, even greatly enhance copper-H_2O_2 induced damage of calf thymus DNA. These results demonstrate strong copper chelating and weak hydroxyl radical scavenging activities which may vary depending on the preparation procedures used for yam rhizome extract [36].

12.3.7 Delayed Aging

Dioscorea species have been traditionally used in treatment of memory-related diseases, such as Alzheimer's disease and other neurodegenerative diseases. Studies revealed that $CHCl_3$ soluble extract from *D. opposite* improved spatial learning and memory performance of mice via Morris water maze and passive avoidance tests. The in vitro pretreatment of primary cultured cortical neurons of rats with the extract demonstrated significant neuronal protection against glutamate- and H_2O_2-induced neurotoxicity of primary cultured cortical neurons of rats. The in vivo and in vitro results suggest that *D. opposite* reveals neuronal protection on the memory impairment associated some neurodegenerative diseases [37]. In our lab, yam tuber (*D. alata* L. var. *purpurea*) administered to senescence accelerated mice (SAMP8) showed that yam significantly improved learning and memory ability, lowered thiobarbituric acid-reactive substances (TBARS), and reduced brain morphological changes. The lyophilized yam was more effective than the yam dried with hot-air, due to the preservation of more antioxidant phytochemicals [38]. Different concentrations of lyophilized yam supplemented in the diet of SAMP8 reduced the cognitive deterioration (learning and memory), amyloid â (Aβ) accumulation, monoamine oxidase B (MAO) activity and increased total thiol level and superoxide dismutase (SOD) activity in brain at a dose dependent manner [39]. The protective components in yam responsible for delayed aging need to be further studied.

12.3.8 Immunological Activity

D. opposite is considered to be beneficial for improvement of immune functions. Diosgenin, the major steroidal sapogenin contained in the rhizomes of *D. opposite*, may be an active constituent contributing to the biological functions induced by *D. opposite*, including anti-inflammatory, antitumor, and immunomodulatory activities. Administration of diosgenin to ovalbumin (OVA)-sensitized mice, the serum level of IgE was diminished while IgG2a was enhanced. Similar to the profile of antibody production, diosgenin suppressed the expression of interleukin (IL)-4, but enhanced IFN-γ expression by splenocytes [40, 41]. In addition, administration of diosgenin markedly attenuated the intestinal expression of IL-4 and GATA3 in ovalbumin (OVA)-sensitized BALB/c mice. Administration of diosgenin reversed the diminished density of intestinal Foxp3^{+}cells induced by OVA oral challenges and enhanced the expression of IL-10 by Foxp3^{+}cells markedly. These results suggest that the suppressive effect of diosgenin on allergen-induced intestinal Th2 responses is closely associated with an up-regulation of the regulatory T-cell immunity in the inflammatory site [42]. A new polysaccharide (YP-1) purified from *D. opposite* Thunb. Stimulated ConA-induced T lymphocyte proliferation and its branches play a significant role in the enhancement of immunological activity. These pharmacological findings may help to elucidate the use of *D. opposite* Thunb. roots in TCM [43].

12.4 TCM Applications and Dietary Usage

12.4.1 TCM Applications

The tuberous rhizome of yam is pale brown, cylindrical, and twisted. Wild yam has been used medicinally for at least 2000 years in China, Japan, and Southeast Asia. Fresh tuber slices are widely used as functional foods in Taiwan, and the dried slices are used as TCM for strengthening stomach function, improving anorexia, eliminating diarrhea [32], and treating hypothyroidism, nephritis, and diabetes.

12.4.2 Dietary Usages

Yam is a nutritious food found in West Africa, Southeast Asia, and the Caribbean. The fresh tuber is used as a nutritious food in Taiwan, China, Japan, and Southeast Asia. It can be served in raw, fried, boiled, barbecued, roasted, baked and processed into a dessert recipe, cereal powder and noodle.

12.5 Clinical Evidences

Many women seek alternatives to hormonal therapies for the management of menopausal symptoms, including osteoporosis, hot flashes, and Alzheimer's disease. Currently, extract of wild yam (*D. villosa*) applied topically in the form of a cream is the most popular treatment. These preparations are known to contain steroidal saponins, including diosgenin, which has been claimed to influence endogenous steroidogenesis. Komesaroff et al. conducted a double-blind, placebo-controlled, cross-over study in 23 healthy women suffering from troublesome symptoms of menopause. Treatment of yam cream for 3 months, no significant side effects or changes in body weight were observed. Systolic and diastolic blood pressures, levels of total serum cholesterol, triglyceride, HDL-cholesterol, FSH, glucose, estradiol and serum or salivary progesterone were unaffected post treatment. Symptom scores showed no statistical difference on diurnal flushing number and severity, total non-flushing symptom scores, and nocturnal sweating, suggesting that short-term treatment with topical wild yam extract is free of side effects, but appears to have little effect on menopausal symptoms [44]. After ingestion of yam (*D. alata*), serum estrone, sex hormone binding globulin (SHBG), and estradiol were significantly increased without changes in serum dehydroepiandrosterone sulfate, androstenedione, testosterone, FSH, and LH. Free androgen index estimated from the ratio of serum total testosterone to SHBG was decreased. Levels of plasma cholesterol and urinary genotoxic metabolite of estrogen, 16α-hydroxyestrone, were significantly decreased. Lag time of LDL oxidation was prolonged significantly and urinary isoprostane was significantly decreased. For the control subjects fed with sweet potato, all three hormone parameters measured were not changed post intervention. Replacing two thirds of staple food with yam for 30 days improved the status of sex hormones, lipids, and antioxidants, although the exact mechanism is not clear. These effects might reduce the risk of breast cancer and cardiovascular diseases in postmenopausal women [45].

Anxiety and depression are major symptoms in postmenopausal women. Interleukin-2 (IL-2) has recently been implicated as a modulator of neuronal function. Anxiety levels in rats are correlated with IL-2 levels in brain. Ho et al. found that anxiety behavior in EPM (elevated plusmaze) was increased in half of ovariectomized (OVX) rats. After chronic treatment with *Dioscorea* (*D. L. alata.* Var. *purpurea* Tainung No. 1), a decrease in anxiety and IL-2 levels were observed in

HA (high anxiety) OVX rats. Despair behavior in the FST (forced swim test) was inhibited by the highest dosage of *Dioscorea*. The OVX-induced anxiety and changes in neuroimmunological function in the cortex reversed by *Dioscorea* suggest that yam is beneficial for alleviating anxiety and depression in postmenopausal women [46].

Generally, decreased skeletal bone mass owing to estrogen deficiency after menopause leads to osteoporosis [47]. Vascular VEGF-A plays an important role in bone-related angiogenesis, a critical process occurs during bone formation and fracture healing. Yen et al. found that diosgenin, extracted from the root of a wild yam (*D. villosa*), elevated VEGF-A mRNA and protein expression in murine MC3T3-E1 preosteoblast-like cells in a concentration dependent manner. The estrogen receptor binding assay revealed that diosgenin interacted with estrogen receptor. In addition, diosgenin up-regulates VEGF-A and promotes angiogenesis in preosteoblast-like cells by a hypoxia-inducible factor-1α–dependent mechanism involving the activation of src kinase, p38 MAPK, and Akt signaling pathways via estrogen receptor. Diosgenin not only generates angiogenic activity in mouse MC3T3-E1 osteoblasts by elevating VEGF-A levels, but also induces VEGF-A up-regulation through activation of HIF-1 by the estrogen receptor-dependent PI3K/Akt and p38 MAPK signaling pathways. This study provides a further insight into the possible therapeutic use of diosgenin for the treatment of certain bone-related diseases or alleviating osteoporosis in menopausal women [48].

12.6 Safety Evaluation and Toxicity Issue

Liao et al. evaluated the toxicity of yam tuber powder at a single high dose and a 28-day continuous feeding in SD rats. They found that a single dose of 5000 mg/kg BW of yam tuber powder revealed no death or toxic effect in rats. The LD_{50} of acute oral feeding appears to be greater than 5000 mg/kg BW in rats. In a 28-day study, yam tuber powder was fed daily by gavage to each treated group consisting of 10 male and 10 female rats with doses of 0, 500, 1000, and 2000 mg/kg BW for 28 days. No significant changes related to the yam tuber powder were evaluated by clinical observation, mortality, body and organ weights, food consumption, ophthalmology, hematology, biochemistry and pathology. According to the results, the no observed adverse effect level (NOAEL) of yam tuber powder in the 28-day feeding toxicity (by gavage) is greater than 2000 mg/kg BW in rats. Therefore, long-term supplementation with yam tuber powder is safe in mammalian [49]. Grindley et al. investigated the protective effects of yam (*D. cayenensis*) on diabetic nephropathy in streptozotocin-induced diabetic rats. They found that malic enzyme activity was significantly reduced in diabetic rats on normal diet and feeding of yam raised the activity of malic enzyme towards normal. Alanine transaminase in the kidney of diabetic rats fed with yam extract was shown to be significantly higher than that of healthy controls. These results demonstrate an overall aggravation of diabetic nephropathy by yam, suggesting that a dietary staple of yam may be a factor associated with the prevalence of diabetes mellitus and the development of renal disease [50]. Moreover, yam sapogenin extract was reported to adversely affect the integrity of kidney membrane [27]. Rubbing the skin with yam can cause allergic contact dermatitis [49]. Yam may also induce asthma [51]. Large doses of yam taken orally may produce emesis. Yam is not recommended for pregnant women because it is considered to induce uterine contractions [52]. In addition, yam is not traditionally used or recommended for consumption during childhood [53].

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