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Could consumption of yam (*Dioscorea*) or its extract be beneficial in controlling glycaemia - A Systematic Review

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Abstract

Yam (*Dioscorea spp.*) and its associated extracts have been shown to possess a variety of biological activities and identified as beneficial in the control of glycaemia in patients with Type II Diabetes Mellitus (T2DM). The objective was to conduct a systematic search of the literature to investigate whether yam and its extract can improve glycaemia and whether consumption of yam could be beneficial for managing T2DM. Using the PRISMA guidelines and the PICO framework, three databases (PubMed, Scopus, and Web of Science) were searched using a key term strategy. Strict inclusion criteria were employed to identify all relevant and available studies. The quality of these studies was assessed using SYRCLE's Risk of Bias tool. Ten studies were included; and all studies consisted of findings from rodent models of diabetes, including animals consuming high fat diets or genetic models of diabetes. All ten studies showed that consumption of yam and/or its extract (containing dioscin, dioscorin, diosgenin, DA-9801/02, or Chinese yam polysaccharides) improved glycaemia. These included improvements in fasting blood glucose and reductions in glucose and increase in insulin levels following a glucose tolerance test. Furthermore, significant changes in body weight and adiposity were observed in nine studies, these included improvements in lipid biomarkers in four and reductions in inflammatory markers in one. The current work indicates that the consumption of yam or its extracts can be beneficial for improving blood glucose however the molecular mechanism for these effects remain largely unknown. Future trials on human subjects are warranted.

Keywords: Yam, Dioscorea, type II diabetes, high fat diet, glycaemia, rodent

Introduction

Diabetes Mellitus (DM) is a non-communicable metabolic disease projected to affect 366 million by 2030 (Saeedi et al. 2019; IDF 2019; Wild et al. 2004). The most common form of diabetes is Type II diabetes (T2DM) which often begins with obesity associated with insulin resistance and glucose tolerance leading to hyperglycaemia, impaired β-cell function, and a decrease in insulin secretion (Colledge et al. 2010). Furthermore, impairment in lipid and lipoprotein metabolism, increase oxidative stress, diminished vascular endothelial function and high blood pressure are also common in T2DM (Erion et al. 2016; Dhananjayan et al. 2016). Chronic exposure to these complications often leads to health conditions including peripheral neuropathy, retinopathy, and nephropathy alongside an increased mortality rate (Constantino et al. 2013).

Therefore, controlling blood glucose is important to prevent diabetic complications and to improve health of patients. While a number of hypoglycaemic agents have been developed, based on current understanding of the pathophysiology of T2DM, their use results in a myriad of side effects and the initial improvements in glycaemia are usually not sustained (Haak et al. 2017; Giorgino et al. 2005).

Obesity is a risk factor for the development of T2DM, and dietary management is thought to reduce the burden on islet cells and thus improve glucose levels, inflammation, and lipid profile (Wu et al. 2014). Recent evidence suggests that the regular consumption of foods with bioactive compounds may benefit health related to prevention or management of chronic diseases (Samtiya et al. 2021; Rinaldo 2020; Mirmiran et al. 2014).

Yam (*Dioscorea*), an angiosperm (flowering plant) not botanically related to sweet potato (*Ipomoea*), is commonly consumed in the Asian and African continents (FAO 2018). In the African populations, the prevalence of T2DM is ranges from 3.5% in rural area to 7.5% in urban area (Uloko et al. 2018; Gatimu et al. 2016). In Asia, yam has been used in Traditional Chinese medicine (TCM) as a natural medicine for T2DM (Jia et al. 2003).

Of particular interest in this region are the numerous extracts, which include allantoin, dioscorin, sapogenins, prosapogenin, gracillin, choline, L-arginine, polysaccharides and proteins. Several *in vitro* and *in vivo* studies have highlighted the anti-diabetic action of a number of these extracts, including dioscorea ethanol extract (Maithili et al. 2011), total saponins (Guo et al. 2016; Yu et al. 2015; Niu et al. 2010, McAnuff et al. 2005) allantoin (Go et al. 2015; Amitani et al. 2015), water soluble polysaccharides (Estiasih et al. 2018), DA-9801 (Lee et al. 2019) and Diosgenin (Ghosh et

al., 2014; Ghosh et al. 2012). However, many of these studies have been conducted in animal models in which diabetes was induced by streptozotocin (STZ) (Guo et al. 2016; Yu et al. 2015; Niu et al. 2010; McAnuff et al. 2005) or alloxan (Estiasih et al. 2018; Maithili et al. 2011). These are popular methods but induce hyperglycaemia via the destruction of the pancreatic islets and does not mimic the insulin resistance presented in human patients with T2DM (Islam et al. 2012).

Therefore, we conducted a systematic review to search the literature to investigate whether yam and its extract can improve glycaemia in diet-induced and spontaneous T2DM *in vivo* models and determine whether the consumption of these could be a diet modification.

Method

The review was constructed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2015).

Searching Strategy

A computerised search of the literature was performed using three databases (PubMed, Scopus and Web of Science) between April 2020 and June 2020. The searching process followed the Population (P), Invention (I), Comparison (C) and Outcome (O; PICO) framework. The population was T2DM animal models or human patients diagnosed with T2DM, the intervention was yam or yam extracts in comparison to controls who do not receive the intervention and the measuring the outcome is the effect of the yam intervention on complications associated with T2DM such as insulin sensitivity and glucose tolerance. Search of terms was conducted through the literature to define the keywords; yam OR "yam extract" OR *Dioscorea* AND diabetes OR antidiabet* OR glycaem* OR insulin OR glucose OR T2DM. Two independent reviewers (WA & AM) assessed the titles, abstracts, and full articles, based on strict inclusion and exclusion criteria, any disagreements with the section of the article were resolved through discussion. Full articles of the selected titles were retrieved and the reference lists of these were searched to identify any additional publications.

Selected Studies Criteria

All related articles from inception were considered as there have been no previous systematic reviews conducted to investigate the relationship of yam and its phytochemicals to the anti-diabetic effects identified during our search.

Inclusion criteria

- Only articles written in English were eligible to avoid any misleading translations.
- All studies must have described either animal models with diet induced T2DM or human participants who have been diagnosed with T2DM by a medical profession.
- Any Yam and yam extracts were considered.
- All studies must have a measure of glycaemic parameters.
- Randomised Clinical Trials (RCT).
- Fully published studies.

Exclusion criteria

- Chemically induced hyperglycaemia using pharmaceutical agents (e.g., streptozotocin)
- Non-diabetic model.
- *In vitro* cell studies exploring the cellular mechanisms.
- Systematic Reviews or critical reviews.
- TCM or any traditional medicine that contains other plants in addition to or alternative to Yam.

Measured Outcomes

The primary outcomes of this review are the effect on glycaemic parameters such as fasting blood glucose (FBG), haemoglobin A1c (HbA_1c), glucose tolerance test (GTT), insulin levels, homeostatic model assessment of insulin resistance (HOMA-IR), insulin-glucose ratio (IGR), insulin sensitivity index (ISI), insulin tolerance test (ITT), metabolic clearance rate (MCR) and adiposity insulin resistance index (Adipo-IRI). While secondary measurements were factors associated with glycaemic control. These include body weight, lipid profile (total fat (TF), white adipose tissue (WAT), total cholesterol (TC), triglyceride (TG), low (LDL) and high(HDL) - density lipoprotein and Free Fatty Acids (FFA)), blood pressure (Systolic (SBP) and diastolic (DBP)) and inflammatory parameters (leptin, interleukin (IL) – 1β, IL-10, Matrix metalloproteinase (MMP), Nuclear factor kappa B (NF-κβ)).

Data extraction

A standard data extraction form as used to obtain data from the studies and charted using Excel (Microsoft excel, Washington, USA). Data extracted included title, author, publication year, country, study population, sample size, diabetic model, exposure to yam genus or yam extracts and outcomes (FBG, HbA_1c, glucose levels following GTT, insulin levels, HOMA-IR, MCR and Adipo-IRI), body weight change, lipid profiles (TF, WAT, TC, TG, LDL and HDL and FFA), blood pressure (SBP and

DBP), and inflammatory parameters (leptin, IL-1β, IL-10, MMP, NF-κβ)). The results from each study alongside statistical outcomes were also extracted.

Data analysis

The relevant results were expressed in tables. The key characteristics of the selected papers included the study design, population, model used, number of the sample, outcome measures and doses of intervention groups. The significant effects in repose to the intervention was charted to compare across the article retrieved. Raw values for the primary outcome measures were not reported consistently across all studies; therefore, we were unable to compare the magnitude of the effect on the primary outcome measures and conduct a meta-analysis.

Quality Assessment

The SYRCLE's Risk of Bias (RoB) tool was used to assess quality assessment due to the lack of human participant studies. This is an adapted version of the Cochrane RoB tool (Higgins et al. 2011) consisting of 10 items relating to 6 types of bias. Items 1, 3, 8, 9, 10 are adopted from the Cochrane RoB tool while items 2, 4, 5, 6, 7 have been adapted or replaced to allow for appropriate assessment of animal studies (Hooijmans et al. 2014; Table S1). Signalling criteria were used to determine and assign a judgement of low, high, or unclear risk of bias.

The quality assessment examined multiple types of bias; selection, performance and direction, attrition and reporting. Selection bias (Items 1,2,3) was assessed by sequence generation, baseline characteristics and allocation concealment. Performance bias (item 4 ,5) was assessed by randomised housing and blinding relating to researchers and/or animal caregivers. Detection bias (item 6, 7) assessed any random outcome assessment and blinding as it can lead to multiple types of bias. Attrition bias (item 8) was explored by assessing incomplete outcome data while reporting bias (item 9) assessed selective outcome reporting. Other sources of bias were covered by item 10 (Table S1).

Results

Eligibility of studies

Using three electronic databases (PubMed/Medline, Scopus and WoS), we identified 967 papers published between 1962 to April 2020. Following the removal of duplicates and an initial title screen, 215 studies were assessed in more detail. Of these 58 were evaluated against stringent inclusion/exclusion criteria; 34 used medically induced diabetic models, 7 utilised a mixture of compounds which contained extracts from sources other than yam, 7 did not measure glucose levels and 4 did not include yam. This left 10 studies eligible for inclusion (Figure 1).

Quality assessment

All 10 papers had 'Fair' as a final judgement for quality (Table 1 and S1). Based on the assessed bias criteria, Moon et al. (2014) was the only study that scored 'High Risk' at the 'Selection Bias' questions 1, 2, 3. While 'Performance and Detection bias' questions 4 and 6 had unclear and low risk in all studies, question 5 and 7 which assess the blinding for caregiver and investigators were judged as 'High Risk'; however, this may not affect the overall judgement where Hirst et al. (2014) found in their meta-analysis that blinding in animal trials is not statistically significant. In regard to 'Attrition Bias', question 8 highlighted two papers as 'High Risk' which are Xu et al. (2020) where eight out of 10 mice outcomes data were reported and Cheng et al. (2019) where eight out of 14 mice outcomes data were reported.

Study Characteristics

The characteristics of the studies are summarised in Table 2. The selected studies were located in Asian countries, though no restraints were placed on location. The experimental length varied from 4 weeks to 19 weeks with an average of 11 weeks. No studies included human participant diagnosed with T2DM, all studies were carried out in rodent model, although two studies utilised *in vitro* models as part of their study design (Xu et al. 2020; Moon et al. 2014). In the rodent model T2DM was induced by consuming high fat diet (HFD) in rats or mice, the KK-A^y mice, which spontaneously exhibit T2DM and the *db/db* mice, a genetic model of T2DM were fed HFD, while the OLETF mice fed normal diet; one study, Hsu et al. (2007) fed the rodent model rats with high fructose diet to induce hyperglycaemia. The studies utilised a variety of *Dioscorea* species although two studies (Li et al. 2019; Shih et al. 2015) did not mention the yam species. A variety of yam extracts were used in nine of the studies; these included components, Dioscin (Xu et al. 2020; Li et al. 2019), Dioscorin (Wu et al. 2018; Shih et al. 2015), Diosgenin (Hashidume et al. 2018), DA-9801

and DA-9802 (Moon et al. 2014; Kim et al. 2012) and *Dioscorea esculenta* powder (Sato et al. 2017); while one study used raw material of *Dioscorea Oppesita,* (a synonym of two species of yam Discorea polystachya and Dscorea oppositifolioa) (Hsu et al. 2007). The yam and/or extracts were obtained via various methods; five articles reported their extraction methods from raw yam (Xu et al. 2020; Moon et al. 2014; Kim et al. 2012; Cheng et al. 2019; Wu et al. 2018) while two articles purchased the yam from external sources (Hashidume et al. 2018; Hsu et al. 2007). The extraction methods included aqueous ethanol extraction from dried yam (Xu et al. 2020; Moon et al. 2014; Kim et al. 2012), water extraction and alcohol precipitation method (Cheng et al. 2019) and raw flush sample mixed with Tris buffer and purified with DE-52 ion exchange chromatography (Wu et al. 2018). These were administered either orally or with saline through gavage at varying doses ranging from 5mg/kg to 100mg/kg. Biochemical measurements included measurements of glycaemia (FBG, GTT, HbA1c, HOMA-IR, IGR, ISI, ITT, MCR and adipo-IRI), lipid profile (TF, WAT, TC, TG, LDL and HDL and FFA), blood pressure (SBP and DBP) and inflammatory markers (leptin, IL-1β, IL-10, MMP, NF-κβ; Table 3 and 4).

Effects of yam extract on measurements of glycaemia

FBG/GTT

All the included studies measured glucose and, although these were measured via a variety of methods (FBG/GTT), they all showed that treatment with either yam or its extract led to significant improvements in glucose tolerance compared to the controls (Table 2). FBG was reported in all studies except Wu et al. (2018) and Shih et al. (2015), while GTT was measured in five of the ten studies (Xu et al. 2020; Wu et al. 2018; Shih et al. 2015; Kim et al. 2012; Hsu et al. 2007). Dioscin, dioscorin, DA-9801, DA-9802, Diosgenin and CYP improved FBG ($P<0.05$), while dioscin, dioscorin, DA-9802 were shown to improve GTT from 30 minutes to 120 minutes after oral or intraperitoneal glucose load ($P<0.05$). The lowest working doses of yam or yam extract ranged from 10-100mg/kg in the HFD model, while in the genetic models of diabetes (KK-A^y, *db/db*, OLEFT) the lowest working doses ranged from 0.5-30mg/kg (Table 3).

HbA1c

HbA1c was measured in two of the ten studies (Xu et al. 2020; Hsu et al. 2007); both showed that consumption of yam or its extract significantly reduced HbA1c. Xu et al. (2020) showed that dioscin reduced HbA1c in KK-A^y at all doses, including the lowest dose of 20mg/kg, although this dose had

no effect on FBG. While Hsu et al. (2007) showed that consumption of *D. Opposita Thunb* had a significant reduction (P<0.05) (Table 3)

Insulin

Fasting insulin levels were measured in three of the ten papers (Xu et al. 2020; Li et al. 2019; Kim et al. 2012) and all showed significant decrease insulin in a dose dependant manner (P<0.05; Table 3). HFD mice treated with Dioscin (10 and 20mg/kg) (Li et al. 2019) or DA-9082 (100mg/kg) (Kim et al. 2012) reduced fasting insulin levels in HFD mice. Dioscin also significantly reduced fasting insulin levels in KK-A^y mice at all three doses 20, 40 and 80mg/kg (Xu et al. 2020).

HOMA-IR, ISI, ITT, IGR, MCR

HOMA-IR was measured in two of the ten studies (Xu et al. 2020; Li et al. 2019), while ISI was measured in one (Xu et al. 2020), ITT was measured in two (Xu et al. 2020; Cheng et al. 2019), IGR was measured in one (Kim et al. 2012) and MCR was measured in one (Sato et al. 2017; Table 3). Administration of the dioscin in HFD mice and KK-A^y significantly reduced HOMA-IR, ISI and glucose following an ITT at all three doses (20-80mg/kg) (Xu et al. 2020), HOMA-IR in Li et al. (2019) reduced in 10, 20mg/kg dioscin groups. While administration of diosgenin in OLEFT mice significantly increased MCR (Sato et al. 2017) and DA-9802 in Kim et al. (2012) reduced IGR significantly. ITT in Cheng et al. (2019) was significant in CYP 20mg/kg.

Adipo-IRI

One study measured adipo-IRI (Li et al. 2019) and showed that dioscin treatment (5-10mg/kg) resulted in significant reduction. (P<0.05).

Other Factors Related to Glycaemic Control

Body weight Changes, Total fats, White adiposity tissue and *Adiposity index*

Nine of the ten studies measured body weight; of these four (Xu et al. 2020; Cheng et al. 2019; Li et al. 2019; Wu et al. 2018) observed a significant decrease in body weight regardless of diabetic model (HFD, KK-A^y or C57BL/6) or yam extract (dioscin, CYP, dioscorin; P<0.05). Li et al. (2019) found that the decrease in body weight following dioscin treatment (10-20mg/kg) was due to a 14% decrease in total fat (p<0.05). However, Hashidume et al. (2018), Sato et al. (2017), Shih et al. (2015), Moon et al. (2014) and Kim et al. (2012) did not observe any changes in body weight nor changes in white adiposity tissue following treatment with sanyaku, diosgenin, dioscorin, DA-9801 and DA-9802 (Table 4).

Lipid Profile (TC, TG, LDL, HDL and FFA)

Five studies (Xu et al. 2020; Li et al. 2019; Cheng et al. 2019; Wu et al. 2018; Hashidume et al. 2018) measured the lipid profile biomarkers, these included TC, TG, LDL, HDL and FFA (Table 4), of these, four found changes in some lipid biomarkers, only Hashidume et al. (2018) observed no differences between treatment and control. Xu et al. (2020), and Li et al. (2019) revealed significant reductions in TC, TG, LDL and FFA following dioscin and treatment ($P<0.05$) in both KK-A^Y and HFD diet mice. These results were partially supported by Wu et al. (2018) and Cheng et al. (2019), while they observed significant reduction in TC and LDL following dioscorin and CYP treatment respectively in HFD model, no changes in TG were observed. In addition, both Xu et al. (2020) and Cheng et al. (2019) found that dioscin and CYP also increased HDL levels.

Blood Pressure

Systolic (SBP) and diastolic (DBP) blood pressure was measured in only one of ten studies. Shih et al. (2015) showed a significant decrease in SBP ($P <0.05$), but not DBP (Table 4)

Inflammatory markers

One of the ten studies measured markers of inflammation and adipocytokines, these included leptin, IL1β, IL-10, MMP and NFκB. Cheng et al. (2019) showed that administration of CYP induced a significant decreased all the markers suggesting an anti-inflammatory effect of CYP (Table 4).

Discussion

The number of people suffering from T2DM is increasing worldwide and has become a global public health problem. New treatment strategies are increasingly needed, and many studies have indicated that natural food constituents, such as resistance starch and bioactive compounds (e.g. phytochemicals), could be incorporated into a healthy balanced diet to aid in the prevention or management of T2DM.

Yam (*Dioscorea* spp.) is the fourth most important tuber crop after potatoes, cassava and sweet potatoes and contains a good source of essential dietary supplements such as protein, well-balanced essential amino acids, and many dietary minerals (Padhan et al. 2020; Zhang et al. 2014). Recently interest has focused on yam as a potential insulin mimetic, thus we searched the current literature to investigate whether yam and/or its extracts has the potential to help manage T2DM. We observed that consumption of yam and/or its extracts had a beneficial effect on numerous glycaemic parameters including FBG, insulin, Hb1Ac, HOMA-IR. Additionally consumption of yam and/or

extracts helped improvements in adiposity and circulating lipids, which are known to influence the development of T2DM.

However much of the work conducted on the effects of yam on T2DM has been shown in animal models and therefore further research is required in human participants, although Jimoh et al. (2008) has shown that consumption of brown yam flour improved glycaemia in healthy subjects compared to other yam flours. In this review, we focused on studies conducted in models in which T2DM was induced by diet or in animals genetically predisposed to developing T2DM rather than those in which diabetes was induced by an injection of STZ, which is a model of type 1 diabetes. High fat feeding in mice leads to obesity, hyperinsulinemia and altered glucose homeostasis due to insufficient compensation by islets, thus modelling the human situation more accurately (King 2012), while STZ administration damages pancreatic β-cells depicting type 1 diabetes (Graham et al. 2011). However, we also included rodent models in which T2DM develops spontaneously this included the OLEFT model, in which animals inherit diabetes, KK-A^Y mice that develop obesity and severe hyperinsulinemia (Tomino 2012), again mimic human predisposition to diabetes. Furthermore, in these models insulin sensitivity can be reversed via dietary manipulation and/or pharmacological administration as well as enable us to understand possible mechanisms (Tomino 2012).

All papers identified in this review showed that consumption of yam and/or extract at various doses improved glycaemia by improving fasting glucose levels and insulin sensitivity. As mentioned earlier starch is the most abundant component of yam; cooking alters the properties of the starch making it more resistant to digestion. Resistant starch has been shown to prevent hyperglycaemia and reduce the risk of diabetes, (Rinaldo 2020; Raigond et al. 2015; Birt et al. 2013) and lower serum triglycerides and LDL cholesterol due to reduction in fat absorption (Nishimura et al. 2011; Shujun et al. 2008). However, all studies identified in this review used extracts to treat the rodents, thus it is unlikely that an increase in resistance starch was responsible for the observed effects, but does highlight that consumption of yam or its extract has similar effects on glycaemia.

Another possible reason for the observed improvements in glycaemia maybe due to the inhibition of α-glucosidase; indeed yam and its extracts have been shown to be potent inhibitors of this enzyme (Ghosh et al. 2014; Zhang et al. 2011). α-glucosidase is located on the brush border of the small intestine and breaks down starch to glucose, and many α-glucosidase inhibitors, such as quercetin and acarbose, have been developed into clinical drugs to reduce blood glucose levels (Yang et al.

2015; Ma et al. 2010; Kado et al. 1998; Vasselli et al. 1993). Not only do these inhibitors reduce fasting blood glucose (Van De Laar et al. 2005) they also reduce postprandial hyperglycaemia thus reducing Hb1Ac (Padhi et al. 2020). However, only two of the eight studies measured this, but both found significant decreases (Xu et al. 2020; Hsu et al. 2007). These inhibitors can also influence the release of the incretin glucagon like peptide 1 (GLP-1), in support Go et al. (2015) showed that allantoin (a yam extract) can increase GLP-1 release in a rat model of streptozotocin induced diabetes. Indeed, we found that yam and/or extract treatment led to a decrease in plasma insulin in the three studies, which measured insulin levels (Xu et al. 2020; Li et al. 2019; Kim et al. 2012). Furthermore, these inhibitors can reduce lipid deposition and reduce adipocyte size and TG and LDL (Go et al. 2015; Kado et al. 1998; Vasselli et al. 1993); indeed, we observed reductions in TG, LDL, FFA and TC in five of the ten studies (Xu et al. 2020; Li et al. 2019; Cheng et al. 2019; Wu et al. 2018; Hashidume et al. 2018). Thus, further supporting the notion that consumption of yam and/or extracts results in the inhibition of α-glucosidase to exert its effects. However, the potency of inhibition of α-glucosidase by yam and/or its extract is dependent on the solvent used for extraction (Ghosh et al. 2014; Zhang et al. 2011) and may be one of the reasons why there was difference in the lowest working dose observed in the studies, even when the same yam extract was utilised. Indeed Xu et al. (2020) used sodium carboxymethyl cellulose, while Li et al. (2019) used saline to dissolve dioscin.

Other modes of action that yam and/or its extracts could improve glycaemic parameters is via the amelioration of oxidative and inflammatory responses. Consumption of high fat diets and high lipid profile levels can lead to the development of oxidative stress and systematic inflammation (Tan et al. 2019), which results in decreased insulin sensitivity leading to hyperinsulinemia and hyperglycaemia causing a pre-diabetic state. If uncontrolled, this can hinder the ability of the β-cells to meet demand leading to the development of diabetes (Manna et al. 2015). This further exacerbates oxidative stress and inflammation leading to complications such as hypertension (Ormazabal et al. 2018). Numerous studies support the notion that yam and/or its extracts have antioxidant and anti-inflammatory properties (Chiu et al. 2013; Jin et al. 2011; Jin et al. 2010)

Indeed, we found that treatment with CYP was found to decrease pro-inflammatory markers NF-Kβ, MMP-3, IL-1B, and anti-inflammatory marker IL-10 (Cheng et al. 2019). IL-10 increases with obesity to protect against the disruption of insulin signalling, thus Cheng et al. (2019) concluded that CYP acted to reduce pro-inflammatory cytokines rather than stimulate anti-inflammatory cytokines. Extracts from *D. batatas* decrease the expression of pro-inflammatory cytokines Tumour necrosis

factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1) and IL-6 in obese rodents (Gil et al. 2015). In addition, the levels of peroxisome proliferator-activated receptors γ (PPARγ) coactivator 1α (PGC-1α) in the pancreas return to basal expression levels in those animals of normal weight, similar to the effects of the drug metformin (Ma et al. 2020). PGC-1α deficiency in the pancreas leads to an increase in pro-inflammatory markers production via NF-KB, which in turn can lead to further damage of the pancreatic tissue (Rius-Pérez et al. 2020).

In support of the antioxidant properties, we found a decrease in Hb1Ac in two of the eight studies (Xu et al. 2020; Hsu et al. 2002). Hb1Ac is a known marker associated with increased oxidative stress (Palem and Abraham 2015). In addition, we observed in one study that treatment with Dioscorin resulted in a decrease in systolic blood pressure possibly via angiotensin converting enzyme and vasorelaxation (Shih et al. 2015; Hsu et al. 2002). Many studies have implicated oxidative stress in hypertension, as reactive oxygen species (ROS) influence vascular, renal and cardiac function and structure (Loperena et al. 2017). Further evidence of antioxidant/anti-inflammatory properties arises for the fact that yam and/or extract can restores the activity of the Phosphoinositide 3 kinase/Protein Kinase B (Akt) and PPARγ pathways, both known to be supressed in diseases associated with oxidative stress and inflammation (Li et al. 2019). Additionally, Cai et al. (2018) reported that *Sanggua Drink* extract, which consists of *Discorea*, might alleviate insulin resistance in HFD fed rodents via the induction of the PI3K/Akt signalling pathway.

The antioxidant/inflammatory properties of yam and/or its extracts may be due to the high phenolic and flavonoid content (Obidiegwu et al. 2020); these phenolic and flavonoids can reduce ROS and reactive nitrogen species (RNS) protecting pancreatic β-cells disruption (Zraika et al. 2006). Indeed, dioscorin has both dehydroascorbate reductase and monodehydroascorbate reductase activity enabling the generation of ascorbate which in turn to reduce the levels of ROS (Hou et al. 1999), thus proposed to be a good reducing agent. Furthermore, in STZ treated mice both allantoin or diosgenin can increase superoxide dismutase (SOD) activity and the levels of reduced glutathione suggesting a reduction in oxidative stress. Moreover, allantoin treatment in STZ rats has been shown to reduced β-cell granulation suggesting that yam may play a potential role in protecting β-cells function and preventing granulation.

Many of the studies focused on the effects of yam and/or its extract on diabetes have investigated the indirect mechanism of improving glycaemia as discussed above. However, evidence for whether

yam and/or its extracts have direct effect on the pancreatic β-cells or other cell types is limited, despite some evidence of a possible direct mechanism. Pancreatic lipase is released from the pancreas causing a reduction in the absorption and digestion of dietary triglyceride. *D. opposite* has been shown to inhibit pancreatic lipase secretion to a similar level to orlistat (the only FDA approved drug that inhibits pancreatic lipase to prevent 30% for fat absorption) (Kim et al. 2016; Seyedan et al. 2015; Yang et al. 2014). This could be associated with changes in lipid profile observed in five of the studies (Xu et al. 2020; Li et al. 2019; Cheng et al. 2019; Hashidume et al. 2018; Wu et al. 2018) and decrease in body weight observed by four of the studies (Xu et al. 2020; Cheng et al. 2019; Li et al. 2019; Wu et al. 2018). Further evidence for direct effects on the pancreas is the ability of yam, particularly *D. batatas* and allantoin, to prevent the loss of pancreatic mass by protecting against loss of islets, structural damage and atrophy in STZ-HFD mice (Ma et al. 2020; de Salgado Rêgo et al. 2014); however, this effect could potentially be indirect via amelioration of inflammation and oxidative stress, thus warrants further studies. There is also evidence that yam and/or its extracts improves glycaemia via improvements in adipose and muscle tissue. Dioscin and *D. batatas* administration decreases visceral adipose tissues and lipid profile, although this is thought to be via the improvements in inflammation. Interestingly there is evidence of direct effects on muscle by Niu et al. (2010), administration of allantoin improved glucose uptake in skeletal muscle isolated from STZ-diabetic rats, possibly via increased translocation of glucose transporter (GLUT) 4, leading to increased MCR as suggested by Sato et al. (2017). Furthermore, administration of *D. batatas* or allantoin in STZ-diabetic rodents increased microfiber number and area. It is well known that insulin resistance is manifested by a decrease in insulin stimulate glucose uptake in skeletal muscle. Nonetheless, the mechanism by which yam and/or extracts influences this is unknown and warrants further investigation.

Limitation

While all the studies identified in this review and others conducted in STZ-rodents agree that consumption of the various yam and/or extracts improve diabetic outcomes, there are some limitations to the study. These include not being able to agree on one species of yam or extract, or specific dose or length of consumption. Furthermore the data extracted from the studies was descriptive and not actual values therefore a meta-analysis was not possible. However, the biggest limitation of this study is the lack of human studies. These are required to determine whether the effects observed in animal studies can be translated, moreover, allow us to assess whether consumption of yam mimics those observed following the consumption of the extracts, to assess

whether the process of cooking yam alters glycaemia and finally to understand whether lifestyle and habitual diet could influence the effects observed.

Conclusion

In summary yam and its extracts have the potential to act as functional foods in the treatment of T2DM in numerous ways. However further studies are required to understand potential mechanisms particularly in understanding the molecular pathways associated with insulin and glucose in the various important tissues (pancreas, muscle, adipose tissue) and to understand whether these are direct or indirect. Furthermore, humans studies are required alongside studies comparing yam to similar to reliably inform dietetic practice, guidelines and policy makers.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Author contributions

W.Z.A, A.M, P.R & P.H.J contributed to the conception, design and drafting of the review. W.Z.A and A.M carried out literature searching, data extraction and analysis. W.Z.A wrote the paper. P.H.J had primary responsibility for the final manuscript.

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Figure legend

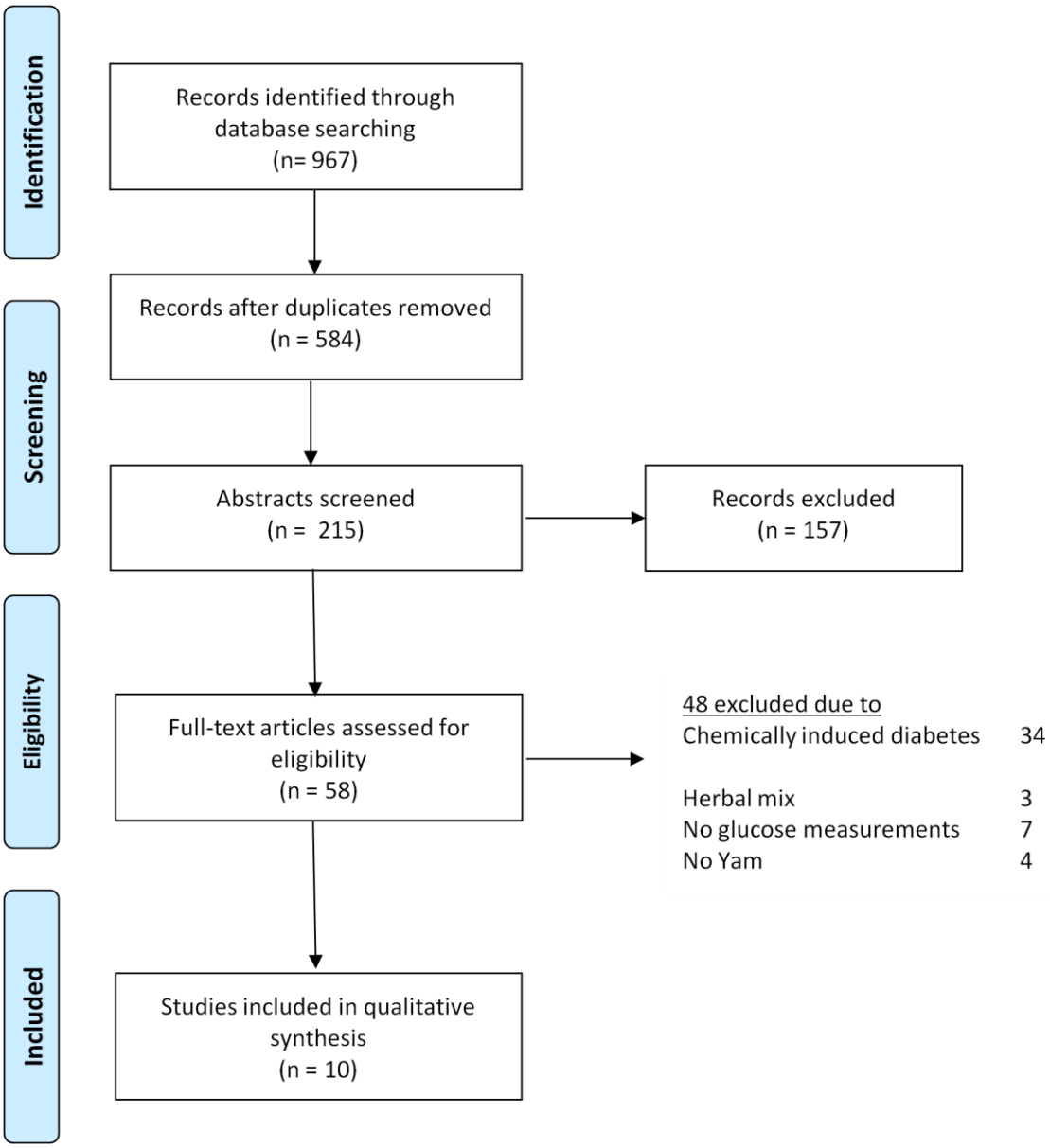

Figure 1 Flow diagram demonstrating the identification and selection of relevant research (PRIMSA., 2015).

Table 1: SYCRLE tool for Risk of Bias (RoB) of selected studies

	Random sequence generation	*Baseline characteristics*	*Allocation concealment*	*Random housing*	*Blinding - caretakers*	*Random outcome assessment*	*Blinding – assessors*	*Incomplete outcome data*	*Selective outcome reporting*	*Other bias*	*Rating*
Xu et al., 2020	?	✓	?	✓	✗	?	✗	✗	?	?	**Fair**
Cheng et al., 2019	?	✓	?	✓	✗	✓	✗	✗	?	✓	**Fair**
Li et al., 2019	?	✓	?	✓	✗	✓	✗	✓	?	✓	**Fair**
Wu et al., 2018	?	✓	?	✓	✗	?	✗	?	?	?	**Fair**
Hashidume et al., 2018	?	✓	?	✓	✗	?	✗	?	?	?	**Fair**
Sato et al., 2017	?	?	?	?	✗	✓	✗	✓	?	?	**Fair**
Shih et al., 2015	?	✓	?	✓	✗	?	✗	?	?	?	**Fair**
Moon et al., 2014	✗	?	?	?	✗	?	✗	?	?	?	**Fair**
Kim et al., 2012	?	✓	?	✓	✗	?	✗	?	?	?	**Fair**
Hsu et al., 2007	?	✓	?	✓	✗	?	✗	?	?	?	**Fair**

? Unclear risk of bias, ✓ Low risk of bias, ✗ **High risk of bias, according to SYCRLE recommendations**

Table 2: Key characteristics of the selected studies

Article	Country of origin	Study design	Animal model		Yam species	Yam/its extract	Mode of administration	Study duration	Biological parameter	Extraction Method
			Diabetic	Control						
Xu et al., 2020	China	RCT	HFD KK-Ay mice	HFD KK-Ay mice	D. nipponica rhizomes	Dioscin	Gavage – OD/ 8wk	8 wks	- FBG, OGTT, HbA_1c - IL, HOMA-IR, ISI, ITT - weight - TC, TG, LDL, HDL, FFA	- 50-60% aqueous ethanol.
Cheng et al., 2019	China	RCT	HFD C57BL/6 mice	HFD C57BL/6 mice	Chinese yam	CYP	Orally – OD/ 8wks	14 wks	- FBG - ITT - weight - TC, TG, LDL, HDL	- Alcohol extraction using water bath - DdH_2O used for washing
Li et al., 2019	China	RCT	HFD C57BL/6 mice	HFD C57BL/6 mice		Dioscin	Gavage – for 12wks	12 wks	- FBG - IL, HOMA-IR, Adipo-IRI - weight - TC, TG, FFA - TF, adiposity index	- Not reported
Wu et al., 2018	Taiwan	RCT	HFD C57BL/	HFD C57BL/	D. alata	Diosc orin	Gavage - OD/ 19wks	19 wks	- OGTT - weight	- Homogenised with Tris buffer

			6 mice	6 mice					- TC, TG, LDL	- eluted with NaCl & dialysed with deionised water
Hashidume et al., 2018	Japan	RCT	HFD KK-Ay mice	HFD KK-Ay mice	D. batatas	Sanyaku Diosgenin	Orally - For 11wks	11 wks	- FBG - weight - TG - WAT	- Diosgenin purchased from Sigma Chemical - Sanyaku purchased in freeze-dried powder form.
Sato et al., 2017	Japan	RCT	OLEFT mice	LETO mice	D. esculenta	Diosgenin	Added to diet with *ad libitum* access	8 wks	- FBG - MCR - weight	- Not reported
Shih et al., 2015	Taiwan	RCT	HFD MW rats	HFD MW rats		Dioscorin	Orally - OD/ 5wks	10 wks	- OGTT - weight - SBP/DBP	- Not reported
Moon et al., 2014	Korea	RCT	HFD *db/db* mice (C57BLKS/J)	HFD *db/db* mice (C57BLKS/J)	D. japonica & D. nipponica	DA-9081	Orally - OD/ 12wks	12 wks	- FBG - weight	- 50% aqueous ethanol. - at room temperature for 48hrs. - Filtered and concentrated.
Kim et al., 2012	Korea	RCT	HFD C57BL/ 6 mice	HFD C57BL/ 6 mice	D. batatas	DA-9082	Gavage - OD/ 7wks	12 wks	- FBG, OGTT - IL, IGR - weight	- Water-ethanol solution for 24hrs.

										- filtered and concentrated.
Hsu et al., 2007	Taiwan	RCT	high fructose diet MW rats	MW rats	D. opposite thumb	D. opposite thumb	Orally through water	4 wks	- FBG, IPTT, HbA_1c	- Purchased from Shen Chang Pharmaceutical Co., Ltd.

RCT: randomised control trial; HFD: high fat diet; MW: male Wister; D.: Dioscorea; CYP: Chinese yam polysaccharides; OD: once daily; wks: weeks; FBG: fasting blood glucose; OGTT: oral glucose tolerance test; HbA1C: glycated haemoglobin; IPTT: intraperitoneal glucose tolerance test; IL: insulin level; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; ISI: insulin sensitivity index; ITT: insulin tolerance test; IGR: insulin-glucose ratio; MCR: metabolic clearance rate; adipo-IRI: adiposity insulin resistance test; TC: total cholesterol; TG: triglyceride; LDL: low density lipoprotein; HDL: high density lipoprotein; FFA: free fatty acids; TF: total fat; WAT: white adiposity tissue; SBP: systolic blood pressure; DBP: diastolic blood pressure, DdH_2O: double distilled water.

Table 3: Effects of yam consumption on glycaemic parameters measured in the selected studies.

Article	Yam/ extract	Model	Dose	Glucose		HbA$_{1}$c (%)	Insulin	IGR	HOMA-IR	ISI	MCR	ITT	Adipo-IRI
				FBG	GTT								
Xu et al., 2020	Dioscin	HFD KK-Ay mice	20mg/kg 40mg/kg 80mg/kg	NS ↓** ↓**	0-120mins ↓**	↓** ↓** ↓**	↓** ↓** ↓**		↓** ↓** ↓**	↓* * ↓* * ↓* *		↓* * ↓* * ↓* *	
Li et al., 2019		HFD mice	5mg/kg 10mg/kg 20mg/kg	NS ↓* ↓*			NS ↓* ↓**		NS ↓* ↓*				↓* ↓** ↓**
Wu et al., 2018	Dioscorin	HFD mice	80mg/kg		30mins ↓** 60mins ↓** 90mins ↓**								

					120mins ↓*								
Shih et al., 2015		HFD rats	50mg/kg		0-120mins ↓*								
Moon et al., 2014	DA-9801	*db/db* mice	30mg/kg 100mg/kg	↓* ↓*									
Kim et al., 2012	DA-9802	HFD mice	100mg/kg	↓*	0-5 min: NS 30-120mins ↓*		↓*	↓*					
Hsu et al., 2007	D. Opposita Thunb.	FD rats	DHW DHW/D. D. 4.2 mg/kg	↓* NS ↓*	↓* NS ↓*	↓* NS ↓*							
Cheng et al., 2019	CYP	HFD mice	10mg/kg 20mg/kg	NS ↓*								NS ↓*	
Sato et al., 2017	Diosgenin	ND OLEFT mice	0.3% added to ND	6wks ↓* 8wks ↓*							↑*		
Hashidume et al.,	Sanyaku	HFD	0.05%	↓*									

2018	Diosgenin	KK-Ay mice	added to HFD	NS									

Arrows indicate direction of change; *, p< 0.05; **, p<0.01; NS: Not significant, HFD: high fat diet; FD: fructose diet; ND: normal diet; FBG: fasting blood glucose, GTT: glucose tolerance test, HbA1c; IGR: insulin-glucose ratio, ISI: insulin sensitivity index, MCR: metabolic clearance rate, ITT: insulin tolerance test, Adipo-IRI: adiposity insulin resistance index

Table 4: Effects of yam consumption on parameters associated with T2DM measured in the selected studies.

Article	Yam/ extract	Model	Dose	Δ Wt.	Lipid profile					BP	Inflammation				
					TG	TC	LDL	FFA	HDL		Lpn	IL1β	IL10	MMP	NF-kB
Xu et al., 2020	Dioscin	HFD KK-Ay mice	20mg/kg 40mg/kg 80mg/kg	↓* ↓* ↓*	↓* * ↓* * ↓* *	↓* * ↓* * ↓* *	↓* * ↓* * ↓* *	↓* ↓* * ↓* *	↑* ↑* ↑*						
Li et al., 2019		HFD mice	5mg/kg 10mg/kg 20mg/kg	NS ↓* ↓*	NS ↓* ↓*	NS ↓* ↓*		NS NS ↓*							
Wu et al., 2018	Dioscorin	HFD mice	80mg/kg	↓*	NS	↓*	↓*								
Shih et al., 2015		HFD rats	50mg/kg	NS						SBP ↓* DBP NS					
Moon et al.,	DA-9801	*db/db*	30mg/kg	NS											

2014		mice	100mg/kg	NS											
Kim et al., 2012	DA-9802	HFD mice	100mg/kg	NS											
Hsu et al., 2007	D. Opposita Thunb.	FD rats	DHW DHW/D. D. 4.2 mg/kg												
Cheng et al., 2019	CYP	HFD mice	10mg/kg 20mg/kg	NS ↓*	NS NS	NS ↓*	NS ↓*		↑* ↑*		NS ↓*	↓* ↓**	↓* ↓* *	↓* ↓**	↓* ↓**
Sato et al., 2017	Diosgenin	ND OLEFT mice	0.3% added to ND	NS											
Hashidume et al., 2018	Sanyaku Diosgenin	HFD KK-Ay mice	0.05% added to HFD	NS	NS										

Arrows indicate direction of change; *, p< 0.05; **, p<0.01; NS: Not significant; HFD: high fat diet; FD: fructose diet; ND: normal diet; ΔWT: change in body weight, TG: Triglyceride, TC: total cholesterol, LDL: Low density lipoproteins, HDL: High density lipoproteins, BP: blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Lpn: Leptin, IL – interleukin, MMP: Matrix metalloproteinases, NF-Kβ: nuclear factor kappa-light-chain-enhancer of activated B cells.