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[Intervention Review]

Sweet potato for type 2 diabetes mellitus

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ABSTRACT

Background

Sweet potato (*Ipomoea batatas*) is among the most nutritious subtropical and tropical vegetables. It is also used in traditional medicine practices for type 2 diabetes mellitus. Research in animal and human models suggests a possible role of sweet potato in glycaemic control.

Objectives

To assess the effects of sweet potato for type 2 diabetes mellitus.

Search methods

We searched several electronic databases, including *The Cochrane Library* (2013, Issue 1), MEDLINE, EMBASE, CINAHL, SIGLE and LILACS (all up to February 2013), combined with handsearches. No language restrictions were used.

Selection criteria

We included randomised controlled trials (RCTs) that compared sweet potato with a placebo or a comparator intervention, with or without pharmacological or non-pharmacological interventions.

Data collection and analysis

Two authors independently selected the trials and extracted the data. We evaluated risk of bias by assessing randomisation, allocation concealment, blinding, completeness of outcome data, selective reporting and other potential sources of bias.

Main results

Three RCTs met our inclusion criteria: these investigated a total of 140 participants and ranged from six weeks to five months in duration. All three studies were performed by the same trialist. Overall, the risk of bias of these trials was unclear or high. All RCTs compared the effect of sweet potato preparations with placebo on glycaemic control in type 2 diabetes mellitus. There was a statistically significant improvement in glycosylated haemoglobin A1c (HbA1c) at three to five months with 4 g/day sweet potato preparation compared to placebo (mean difference -0.3% (95% confidence interval -0.6 to -0.04); P = 0.02; 122 participants; 2 trials). No serious adverse effects were reported. Diabetic complications and morbidity, death from any cause, health-related quality of life, well-being, functional outcomes and costs were not investigated.

Authors' conclusions

There is insufficient evidence about the use of sweet potato for type 2 diabetes mellitus. In addition to improvement in trial methodology, issues of standardization and quality control of preparations - including other varieties of sweet potato - need to be addressed. Further observational trials and RCTs evaluating the effects of sweet potato are needed to guide any recommendations in clinical practice.

PLAIN LANGUAGE SUMMARY

Sweet potato for type 2 diabetes mellitus

Sweet potato (*Ipomoea batatas*) is a plant found in the tropical and subtropical belts and is one of the most nutritious tropical and subtropical vegetables. As well as being popular in cooking in countries in Asia-Pacific, Africa and North America, sweet potato is also used in traditional medicine for the treatment of diabetes mellitus. We decided to investigate whether there is enough evidence from medical trials to show whether sweet potato works as a treatment for diabetes. This review of randomised controlled trials found only three studies (with a total of 140 participants) that evaluated the effects of sweet potato for type 2 diabetes mellitus compared with a fake medicine (placebo). All these trials were of very low quality. Two studies with 122 participants showed improved long-term metabolic control of blood sugar levels as measured by glycosylated haemoglobin A1c (HbA1c) which was moderately lowered by 0.3% in participants who were given 4 g sweet potato tablets a day for three to five months. The duration of treatment ranged from six weeks to five months. No study investigated diabetic complications, death from any cause, health-related quality of life, well-being, functional outcomes or costs. Adverse effects were mostly mild, and included abdominal distension and pain. There are many varieties of sweet potatoes and sweet potato preparations. More trials are needed to assess the quality of the various sweet potato preparations as well as to evaluate further the use of different varieties of sweet potato in the diet of diabetic people.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. *Ipomoea batatas* (Caiapo) tablets compared to placebo for type 2 diabetes mellitus

***Ipomoea batatas* (Caiapo) tablets compared to placebo for type 2 diabetes mellitus**

Patient or population: people with type 2 diabetes mellitus
Settings: out-patients
Intervention: *Ipomoea batatas* (Caiapo) tablets
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	*Ipomoea batatas* (Caiapo) tablets				
Morbidity	See comment	See comment	Not estimable	See comment	See comment	Not investigated
Adverse effects Follow-up: 1.5 to 5 months	See comment	See comment	Not estimable	140 (3)	⊕⊝⊝⊝ **very low** [a]	2 out of 3 studies reported adverse events[b]
Health-related quality of life	See comment	See comment	Not estimable	See comment	See comment	Not investigated
Well-being	See comment	See comment	Not estimable	See comment	See comment	Not investigated
Functional outcomes	See comment	See comment	Not estimable	See comment	See comment	Not investigated
Costs	See comment	See comment	Not estimable	See comment	See comment	Not investigated
HbA1c [%] (final values) Follow-up: 3 or 5 months	Final values for HbA1c across control groups ranged from **6.5 to 7.1**	Final values for Hba1c in the intervention groups were **0.3 lower** (0.6 to 0.04 lower)	-	122 (2)	⊕⊝⊝⊝ **very low** [c]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval;

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: we are very uncertain about the estimate

[a]Downgraded by three due to high risk of bias (insufficient information on the process of randomisation, blinding, selective outcome and incomplete data reporting), small number of trials and participants and no replication of trials by other authors (same investigating team throughout)
[b]Mild gastrointestinal symptoms such as nausea, diarrhoea, constipation, gastric pain and abdominal distension
[c]Downgraded by three due to imprecision, high risk of attrition bias and indirectness

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances in carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy (i.e. problems with the eyes, kidneys and peripheral nerves). Diabetes mellitus also increases the risk of cardiovascular disease. For a detailed overview of diabetes mellitus, please see the 'Additional information' section in the information about the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About', 'Cochrane Review Groups (CRGs)'). For an explanation of methodological terms, see the main glossary in *The Cochrane Library*.

Type 2 diabetes mellitus (T2DM) is a global public health issue (Abegunde 2007; Wild 2004). The increase in numbers of people with T2DM across the age spectrum is of concern. Given the progressive nature of the disease, and the multiple pathophysiological (disease) abnormalities associated with it, accelerated ageing is suspected. This is supported by evidence both at molecular and functional levels (Monnier 2005).

Description of the intervention

Sweet potato (*Ipomoea batatas*) is a member of the Convolvulaceae family; it is a dicotyledonous perennial plant found in the tropical and subtropical belts (Woolfe 1992). Most varieties are edible, and all parts of the plants - shoots, leaves, vine and tubers - are consumed. The large, sweet-tasting tuberous roots, young leaves and shoots are common market vegetables. Sweet potato is rich in nutrients and ranked highest in nutritional value amongst vegetables available in the United States of America (USDA 2010). Among the important nutrients found in tubers are monosaccharides (Salvador 2000), complex carbohydrates (Sabater-Molina 2009), dietary fibre, beta-carotene (a source of vitamin A) (Maiani 2009), vitamin C, vitamin B6, anthocyanins (Miyazaki 2008), and minerals (Antia 2006). The leaves of sweet potato are rich in protein, fibre, fat, vitamins, and minerals (Antia 2006). Linoleic and alpha-linolenic acids (Almazan 1998), galactolipids (Napolitano 2007), and bioactive substances (e.g. dietary antioxidants, including anthocyanins (Islam 2002), polyphenols (Thu 2004), flavonoids (Miean 2001), and caffeic acid derivatives (Islam 2003)) are also present. These compounds have been extensively investigated for their role in health promotion in many countries.

As well as being popular in the cuisines of countries in the Asia-Pacific area, Africa and North America, sweet potato is also used in traditional medical practices for the treatment of T2DM (Duke 1981). In addition, various parts of the plants are used to treat asthma, nausea, fever, tumours, bug bites, burns, upset stomach, diarrhoea, boils, and acne. It is also used as a tonic for lactating women and during convalescence.

Adverse effects of the intervention

There have been anecdotal reports of instances of anaphylaxis after ingestion of sweet potato (Velloso 2004), however, there have been no reports of adverse effects such as hypoglycaemia (low blood sugar levels), weight gain or an increased risk of fractures. Even though there are low levels of toxins in the leaves of sweet potato - phytic acid, tannic acid, and, to a lesser extent, oxalic acid - these can be reduced to negligible levels with conventional blanching (Mosha 1995). Furthermore, microwave blanching also reduces trypsin and chemotrypsin inhibitors, which improves digestibility of proteins (Mosha 1999).

How the intervention might work

The blood glucose-lowering activities of sweet potato were demonstrated in animal studies. A number of bioactive compounds were isolated from the leaves (Li 2009), and also the tubers (Kusano 2001; Sakuramata 2004). These compounds, together with dietary fibre, contribute to blood glucose-lowering activitiy. Besides glycaemic control, sweet potato has shown anti-sclerotic activity and inhibition of glycation in vitro (Miyazaki 2008; Park 2010), as well as antihypertensive (Egert 2009), antioxidative (Huang 2007; Islam 2009), antimutagenic (Kurata 2007), chemopreventive (Wang 2008), and cardioprotective properties (Maiani 2009). Finally, there is a suggestion that sweet potato may delay amyloid formation and prevent neuronal damage in the brain of mice (Kim 2011; Lu 2010; Wang 2010; Wu 2008; Ye 2010).

In clinical terms, the aforementioned properties of the sweet potato plant may not only contribute to glycaemic control, but may also show possible protective effects on target organs. The presence of other biologically-active compounds may have positive impacts on health and well-being of people with T2DM.

Why it is important to do this review

Asia is in the midst of the current T2DM epidemic (Chan 2009). The intense resource requirements of diabetic care, and high quality care of the disabled, coupled with the current epidemic of T2DM, particularly in the developing countries, are of concern. Both cross-sectional and longitudinal studies have demonstrated that T2DM is a risk factor for both cognitive and physical functional limitations and disabilities, especially in older adults (Bruce 2005; De Rekeneire 2003; Gregg 2002; Kalyani 2010; Mogi 2004; Yen 2010). Limitations in activities of daily living and instrumental activities of daily living lead to an increased likelihood of hospitalisation, institutionalisation, and loss of economic self-sufficiency (Abbatecola 2009). Thus, T2DM is a burden to families, the community, and social and healthcare systems.

It has been suggested that proper glycaemic control is a modifiable factor of disability, particularly with respect to those disabilities related to instrumental activities of daily living (Abbatecola 2009). Studies on animal models have demonstrated the protective effect of glycaemic control on beta-cells (Grossman 2010).

A healthy diet consisting of low fat levels, with high levels of complex carbohydrates, appropriate portions of proteins, essential micronutrients and minerals in the therapeutic nutritional management of T2DM has been well-established (Bantle 2008). In the past decade, the enhanced global research into botanicals as potential contributors to the management of T2DM beyond nutritional therapy has identified more than 600 plants that may be helpful (Grover 2002; Li 2004; Malviya 2010; Mukherjee 2006). However, there is currently insufficient evidence to recommend the use of an individual botanical and its products specifically in mainstream medical practice for the management of T2DM.

In addition, there are also concerns of 'botanical'-drug interactions with the concurrent use of oral hypoglycaemics (Genser 2008). Adverse consequences such as severe hypoglycaemia may result if these interactions are not identified and managed properly. Other important longer-term adverse factors that may affect function include weight gain and increase in fracture risk. Should this happen, the cumulative effect of worsening impairments and increasing the risk of disabilities and dependency would aggravate the existing burden of care, and compound the escalating health and social-care costs.

Most of the evidence implicating the influence of sweet potato on glucose-insulin metabolism are preclinical studies and anecdotal case reports. There are still gaps in the knowledge regarding its potential use in the management of T2DM in the clinical context. Apart from the nutritional qualities of the plant, powder, tablets and food supplements containing compounds extracted from sweet potato are also available - all touting its benefit in diabetes management. Better insight into this common botanical may enable clinicians to improve the management of T2DM, complementing 'lifestyle' management.

Given the potentially devastating outcomes of the disease, especially in older adults, addressing the gaps in the literature is important. To date, there has been no literature review specifically investigating the clinical effects of sweet potato in the management of T2DM.

OBJECTIVES

To assess the effects of sweet potato for type 2 diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials.

Types of participants

We included adults over 18 years of age, of either gender, with type 2 diabetes mellitus based on the diagnostic criteria below. Individuals with normal fasting blood glucose and postprandial glucose levels were excluded. People with concomitant endocrinopathy affecting their blood glucose levels were also excluded.

Diagnostic criteria

To be consistent with changes in classification and diagnostic criteria of diabetes mellitus through the years, the diagnosis should have been established using the standard criteria valid at the time of the beginning of the trial (for example ADA 1999; ADA 2008; WHO 1998). Ideally, diagnostic criteria should have been described. If necessary, we used authors' definition of diabetes mellitus. We planned to subject diagnostic criteria to a sensitivity analysis.

Types of interventions

Intervention

Any orally administered mono-preparation of sweet potato in any dose or form. This could be the sole intervention, or given in combination with diet, insulin, oral hypoglycaemic agents, or both.

Control

Placebo or no treatment, with or without diet, active medications, such as insulin, oral hypoglycaemic agents, or other herbal or nutritional preparations.

Co-interventions were considered if both arms of the randomised trial received similar interventions. However, we excluded combination preparations of sweet potato with other nutritional or herbal preparations.

Types of outcome measures

Primary outcomes

- Glycaemic control (fasting blood glucose levels (FBG); two-hour postprandial blood glucose levels; glycosylated haemoglobin A1c (HbA1c)).
- Morbidity (both type 2 diabetes mellitus-related morbidities and cardiovascular-related co-morbidities; all cause morbidity).
- Adverse effects (e.g. hypersensitivity reaction, hypoglycaemia).

Secondary outcomes

- Serum insulin, C-peptide or insulin sensitivity (homeostasis model assessment of insulin resistance (HOMA-IR)).
- Body weight or body mass index (BMI).
- Blood levels of lipids: total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides.
- Functional outcomes (both physical and cognitive functions).
- Health-related quality of life.
- Well-being.
- Costs.

Timing of outcome measurement

Two of the outcomes, fasting blood glucose and two-hour postprandial glucose levels, required trials with durations of at least six weeks, or more, to yield meaningful results. HbA1c trials needed to be run over three months.

Search methods for identification of studies

Electronic searches

We searched the following sources from inception to the present.

- *The Cochrane Library* (2013, Issue 1).
- MEDLINE (until February 2013).
- EMBASE (until February 2013).
- CINAHL (until February 2013).
- LILACS (www.bireme.br/bvs/I/ibd.htm - until February 2013).
- Natural Medicines Comprehensive Database (until February 2013).
- SIGLE (System for Information on Grey Literature in Europe - until 2013).

Theses:

- Proquest Dissertations and Theses database.

For detailed search strategies see Appendix 1.

We also searched databases of ongoing trials (www.clinicaltrials.gov/ and www.clinicaltrialsregister.eu/). We planned to provide information including trial identifiers about potentially-relevant ongoing studies in the table 'Characteristics of ongoing studies' and in a 'Matrix of study endpoints (protocol/trial documents)'. We wanted to find the protocol of each included study, either in databases of ongoing trials, in publications of study designs, or both, and specify data in an appendix 'Matrix of study endpoints (protocol/trial documents)'.

No additional key words of relevance were detected during any of the electronic or other searches. Thus, the electronic search strategies were not modified. Studies published in any language were included.

We sent results of electronic searches to the editorial office of the Cochrane Metabolic and Endocrine Disorders Group for databases to which their staff did not have access.

Searching other resources

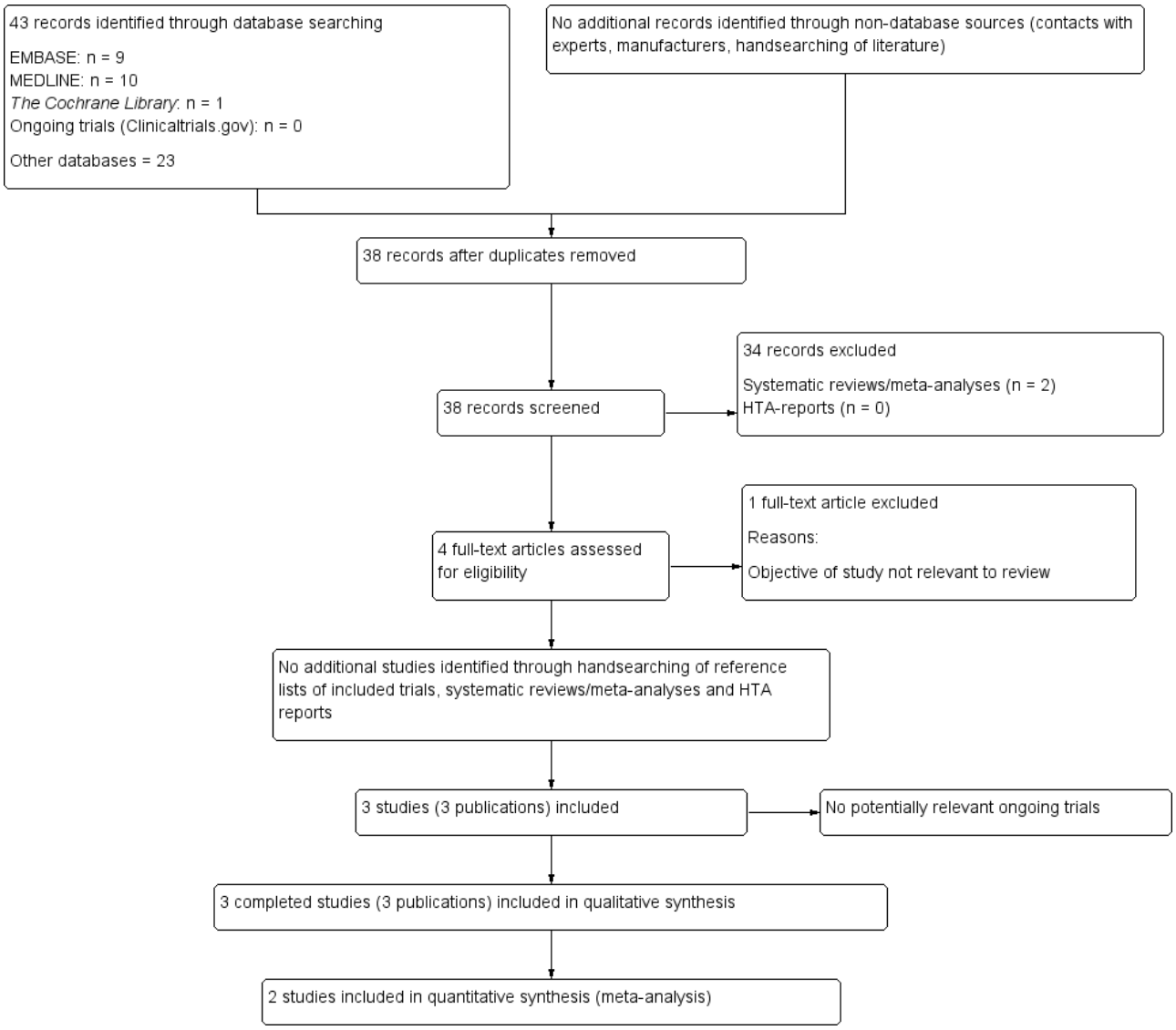
We tried to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses and health technology assessment reports. We approached content experts and associations for further additional information, additional references, unpublished data and/or updated results of ongoing interventions. We also contacted manufacturers of powder, tablets and food supplements that contain compounds extracted from sweet potato for additional information, where necessary.

Data collection and analysis

Selection of studies

To determine which studies should be assessed further, two review authors (CPO, SCL) independently scanned the abstract, title, or both, of every record retrieved. The full text of all potentially relevant articles was investigated. We selected only three studies for inclusion in this review. Where differences in opinion existed, they were resolved by a third party (from the editorial office). Had resolution of a disagreement not been possible, the article would have been added to the 'Studies awaiting classification' section and the study authors would have been contacted for clarification. This process is summarised in the PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart (Figure 1) of study selection (Liberati 2009).

Figure 1. Study flow diagram



Data extraction and management

For studies that fulfilled inclusion criteria, two authors (CPO, SCL) independently extracted characteristics about the relevant population and the interventions using standard data extraction templates (for details see Characteristics of included studies; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11). Any disagreements were resolved by discussion, or, when required, by a third party (editorial office). We attempted to contact the authors for relevant details about the trials. The results of this survey are displayed in Appendix 12.

Dealing with duplicate publications

Should there be duplicate publications and companion papers relating to a primary study, we intend to maximize the yield of information by simultaneous evaluation of all available data.The publication that reported the longest follow-up associated with our primary or secondary outcomes will obtain priority and be marked as the primary reference for that study.

Assessment of risk of bias in included studies

Two authors (CPO, SCL) assessed each trial independently for risk of bias. Disagreements were resolved by consensus, or by consultation with a third party (editorial office).

We assessed risk of bias using The Cochrane Collaboration's tool for assessment of risk of bias (Higgins 2011). We used the following criteria in this assessment.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding (performance bias and detection bias), blinding of participants and personnel assessed separately from blinding of outcome assessment.
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

We judged risk of bias criteria as being at 'low risk', 'high risk' or 'unclear risk', and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We presented a 'Risk of bias' graph (Figure 2) and 'Risk of bias' summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

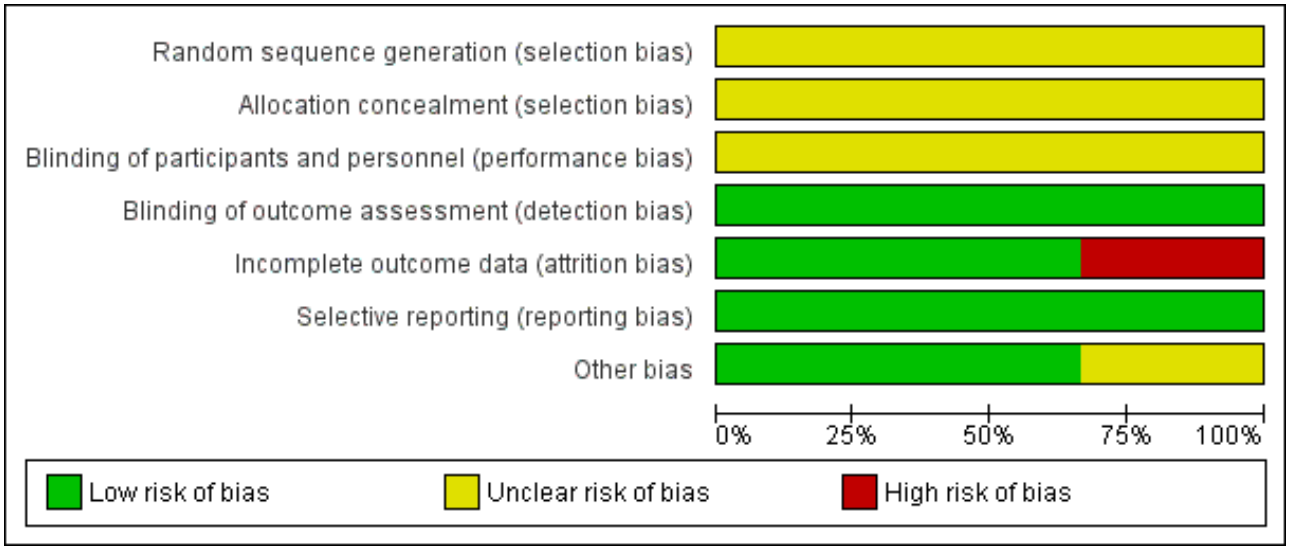
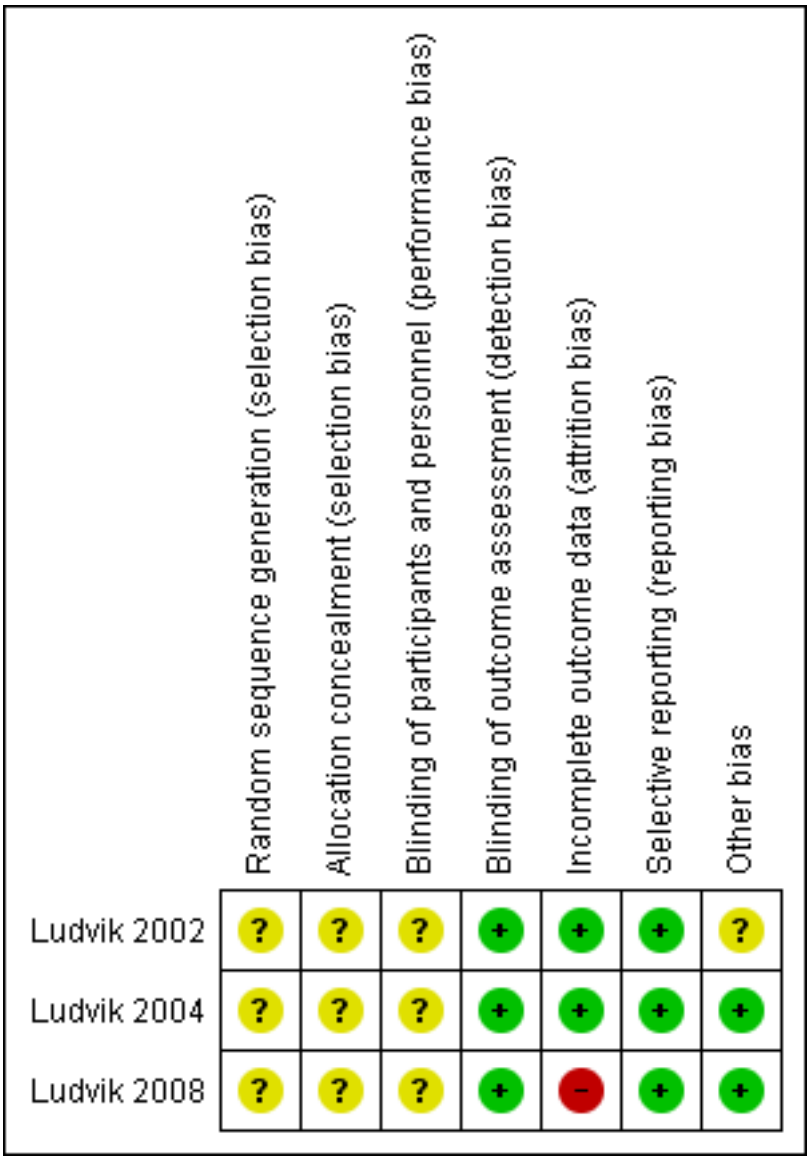


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



We assessed the impact of individual bias domains on study results at endpoint and at study levels.

Measures of treatment effect

We expressed dichotomous data as odds ratios (ORs) or risk ratio (RRs) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MD) with 95% CI.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome.

Dealing with missing data

We attempted to obtain missing data from authors. If it was feasible, we performed careful evaluation of important numerical data such as screened, randomised participants as well as intention-to-treat (ITT), and as-treated and per-protocol (PP) populations. We investigated attrition rates, for example drop-outs, losses to follow-up and withdrawals, and appraised issues of missing data and imputation methods critically (for example last-observation-carried-forward (LOCF)).

Assessment of heterogeneity

In the event of substantial clinical, methodological, or statistical heterogeneity we did not report study results as pooled meta-analysed effect estimates.

We planned to identify heterogeneity by visual inspection of the forest plots and by using a standard Chi^2 test. As this test has a low power, a significance level was set at $\alpha = 0.1$. We specifically examined heterogeneity employing the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); an I^2 statistic of 75% or more indicates a considerable level of inconsistency (Higgins 2011).

When heterogeneity was found, we planned to determine potential reasons for it by examining individual study and subgroup characteristics.

We expected the following characteristics to introduce clinical heterogeneity.

- Compliance with treatment (including medical and nutritional management).
- Co-medications (e.g. insulin, oral hypoglycaemics).

Assessment of reporting biases

If we had identified more than 10 RCTs that investigated a particular outcome, we planned to use funnel plots to assess small study bias. There are a number of explanations for asymmetry in a funnel plot (Sterne 2001), and we planned to interpret results carefully (Lau 2006).

Data synthesis

Unless there was good evidence for homogeneous effects across studies, we planned to summarise primarily low-risk of bias data by means of a random-effects model (Wood 2008). We wanted to interpret random-effects meta-analyses with due consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual study (Riley 2011). Primarily, we summarised data statistically if they were available, sufficiently similar and of sufficient quality. We performed statistical analyses according to the statistical guidelines in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analyses if any one of the primary outcome parameters (see above) demonstrated statistically significant differences between intervention groups.

The following subgroup analyses were planned.

- Studies with normal or below baseline nutritional status.
- Effect of dosage of sweet potato extract or products.
- Effect of forms of sweet potato extract or products.
- Effect of duration therapy of sweet potato extract or products.

We planned to apply tests of interaction to determine subgroup effects (Altman 2003).

We anticipated the direction of the subgroup effects to be as follows (Sun 2010).

- Direction of effect on glycaemic control is reversed for sweet potato extract or products, that is, sweet potato and its products have beneficial effects for those with below baseline nutritional status.
- Direction of effect on glycaemic control is unchanged for the effects of dosage, forms and duration of therapy of sweet potato extract or products.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect sizes.

- Restricting the analysis to published studies.
- Restricting the analysis by taking into account risk of bias, as specified in the section Assessment of risk of bias in included studies.
- Restricting the analysis to very long or large studies to establish the extent to which they dominate the results.
- Restricting the analysis to studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

We also wanted to test the robustness of the results by repeating the analysis using different measures of effect size (RR, OR etc.) and different statistical models (fixed-effect and random-effects models).

RESULTS

Description of studies

For details see Characteristics of included studies and Characteristics of excluded studies. There are no studies awaiting classification.

Results of the search

The original electronic searches identified 12 articles (Figure 1). No additional records or unpublished studies were identified through other sources. We removed four duplicates. On reading the titles and abstracts, we excluded a further four articles because they were reviews and non-clinical studies. This search for the review update identified a total of 31 additional references, however, no new studies were identified.

We selected a total of four publications describing randomised controlled clinical trials for further assessment (Ludvik 2002; Ludvik 2003; Ludvik 2004; Ludvik 2008). Two publications were analyses from the same trial (Ludvik 2002; Ludvik 2003). One of them was published as a 'letter to the editor' (Ludvik 2002), and, therefore, provided limited information. The second publication evaluated the mechanism of sweet potato (Caiapo) (Ludvik 2003). All the trials were published in the English language.

Two trials recruited patients from offices of general practitioners from Austria, Germany and Switzerland (Ludvik 2004; Ludvik 2008). The other trial did not provide information about the setting of the study (Ludvik 2002).

Included studies

Altogether, we included three trials in this review (Ludvik 2002; Ludvik 2004; Ludvik 2008). The details of these trials are summarised in Characteristics of included studies. Participants were recruited from outpatient clinics in Switzerland (Ludvik 2004), Austria and Germany (Ludvik 2008). The third trial did not provide information about the centre of study (Ludvik 2002). All these trials used similar sweet potato tablets, of different dosages, and placebo controls. The duration of treatment ranged from six weeks to five months.

Baseline characteristics

Ludvik 2002 included only male participants, while Ludvik 2008 had a female-to-male ratio of 1:1 that was roughly balanced between the sweet potato (Caiapo) tablets group and the control group. Ludvik 2004 had a female-to-male ratio of 3:5. There was no

information about the duration of diabetes in two trials (Ludvik 2002; Ludvik 2004). In the third trial, the duration of T2DM was 3.5 years (standard deviation (SD) 4.2) and 4.2 years (SD 2.9) for the intervention and control groups, respectively (Ludvik 2008). These publications did not report any relevant baseline data on co-morbidities. A total of 69 patients with T2DM were on dietary control only in the intervention groups and 71 patients in the control groups, respectively.

Participants

A total of 140 participants with T2DM participated in the three trials, ranging from 18 to 61 patients per trial (Ludvik 2002; Ludvik 2004; Ludvik 2008). Most participants were of white complexion. The mean ages were all over 55 years. One trial recruited only male participants (Ludvik 2002), while the other two trials had female-to-male ratios of about 1:1 (Ludvik 2004; Ludvik 2008).

Diagnosis

All trial participants had T2DM. Criteria for diagnosis in all three trials were based on the authors' definitions. With the small number of trials and relatively small sample sizes, sensitivity analysis on diagnostic criteria was not possible.

Treatment before study

All the participants were on diet control prior to the studies. Five patients in one study were on antidiabetic medications in addition to diet control (Ludvik 2004). These drugs included metformin and glibenclamide. There was a washout period of two weeks following withdrawal of the medications. In the trial of Ludvik 2008, medications that affected the blood glucose level (such as corticosteroids, high-dose diuretics or beta-blockers) were stopped during the two weeks prior to screening and for the duration of the entire study. Screening for participants took place one month prior to the start of the studies, and was followed by a washout period of four weeks after withdrawal of hypoglycaemic drugs.

Interventions

Sweet potato (Caiapo) tablets were used as the intervention in all the trials. These tablets came from the same manufacturer and were made from powdered white-skinned sweet potato (*Ipomoea batatas*). One trial used two different dosages of Caiapo tablets (2 g and 4 g) (Ludvik 2002). The other two trials used a 4 g dose of Caiapo tablets (Ludvik 2004; Ludvik 2008). In all three trials, the control interventions were placebos. However, no information was provided about the content of the placebos.

Outcomes

All included trials reported glycaemic control. The parameters included fasting blood glucose and glycosylated haemoglobin A1c (HbA1c). Only one trial reported two-hour postprandial blood glucose (Ludvik 2004). The other outcomes that were reported included lipid levels (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides), body weight, BMI and adverse events. Two of the trials reported details of adverse events (Appendix 9; Appendix 10; Appendix 11). These mild adverse events, i.e. upset stomach, abdominal distention, stomach-ache, and nausea were observed in both the intervention and control groups. No serious adverse events were observed in the intervention groups. One trial observed no adverse events in either the control or intervention groups (Ludvik 2002). All outcomes measured were reported at the end of treatment. Only one trial reported follow-up data at two months (Ludvik 2004). None of the trials reported outcomes on diabetic complications and morbidity, functional outcomes, health-related quality of life, well-being or costs.

Excluded studies

Only one RCT was excluded (Ludvik 2003). Although Ludvik 2003 was an analysis from the same study as Ludvik 2002, its objective was to evaluate the mechanism by which *Ipomoea batatas* worked, therefore, it was not relevant to the objective of this review. Furthermore, it did not contain relevant outcome data. There are no ongoing studies or studies awaiting classification.

Risk of bias in included studies

We detected a predominantly unclear risk of bias in the domains of selection and performance bias within and across studies (see Figure 2 and Figure 3). All the trials were of parallel-group design, but there was limited information on design and methodology.

Allocation

None of the trials reported adequately on randomisation and allocation concealment.

Blinding

Although all trials were described as having been double-blinded, none reported on the double-blinding procedure.

Incomplete outcome data

In two trials, all participants completed the study, and no treatment withdrawals were reported (Ludvik 2002; Ludvik 2004). One trial reported participants lost to follow-up with justifications (Ludvik 2008). However, there was no detail about the number of participants missing from each of the treatment and control groups. None of the three trials provided explicit reporting of intention-to-treat analyses or missing data.

Selective reporting

No selective reporting bias was detected (see Appendix 5; Appendix 7).

Other potential sources of bias

No other potential sources of bias were detected.

Effects of interventions

See: **Summary of findings for the main comparison** *Ipomoea batatas* (Caiapo) tablets compared to placebo for type 2 diabetes mellitus

Comparisons

Similar sweet potato (Caiapo) tablets were used in all the three trials. The comparisons were as follows.

- Sweet potato (Caiapo) tablets 2 g or 4 g daily versus placebo (Ludvik 2002).
- Sweet potato (Caiapo) tablets 4 g daily versus placebo (Ludvik 2004; Ludvik 2008).

The three trials reported outcomes that included fasting blood glucose, glycosylated haemoglobin A1c (HbA1c), total cholesterol,

triglycerides and adverse effects. Ludvik 2002 and Ludvik 2008 reported on BMI, and Ludvik 2004 on body weight.

Primary outcomes

Glycaemic control

Compared with placebo, sweet potato (Caiapo) preparations of 2 g/day showed no statistically significant effect on the reduction of fasting blood glucose when used for two months or less (Analysis 1.1). However, when the dosage was increased to 4 g/day, there were statistically significant reductions in both the short (six weeks to two months) and longer terms (three to five months) (Analysis 1.1). Data for fasting blood glucose of less than three months are not reported as a pooled estimate, as there was a high level of heterogeneity for this outcome (I^2 = 88%). Data from three to five months showed a mean difference in fasting blood glucose between groups of -0.68 mmol/L in favour of the sweet potato intervention (95% CI -0.84 to -0.52; P value < 0.00001; 122 participants; two trials; Analysis 1.1).

Data for two-hour postprandial blood glucose were only available from one publication (Ludvik 2004). There were no statistically significant reductions in two-hour postprandial blood glucose levels with 4 g/day sweet potato tablets compared with placebo at two or three months (Analysis 1.2).

When compared with placebo, the sweet potato treatment showed statistically significant reductions in HbA1c levels (Analysis 1.3). The mean difference for HbA1c was -0.3% (95% CI -0.57 to -0.04; P value 0.02; 122 participants; two trials; Analysis 1.3) in favour of the sweet potato intervention.

Morbidity

No publication presented data on T2DM-related or cardiovascular-related morbidities.

Adverse events

Details of adverse events are described in Appendix 9; Appendix 10; Appendix 11.

Only two out of the three studies reported adverse events (Ludvik 2004; Ludvik 2008). Adverse events were present for both intervention and control groups, and were not specific to the sweet potato intervention groups. In view of the poor quality of the reported data, quantitative analysis was not possible. Most of these reported events were mild gastrointestinal symptoms such as nausea, gastric pain, diarrhoea, constipation and abdominal distension. We were not able to contact the authors for further details (Appendix 12).

No serious adverse events such as severe hypoglycaemia were reported. There was also no explicit reporting of drop-outs due to adverse events.

Secondary outcomes

Serum insulin, C-peptide or insulin sensitivity (homeostasis model assessment of insulin resistance (HOMA-IR))

Two trials provided data on fasting insulin level (Ludvik 2004; Ludvik 2008). The sample size in Ludvik 2002 was inadequate for estimation of any relevant changes. Data disclosed in Ludvik 2008 showed no statistically significant change in the fasting insulin level in the sweet potato treatment group (Analysis 1.4). Furthermore, Ludvik 2008 provided data on the measurement of beta-cell function and insulin sensitivity; after five months of sweet potato tablets, there was a statistically significant improvement in insulin sensitivity but not in beta-cell function (Appendix 13).

Body weight or body mass index

Only one trial provided data on body weight with no BMI data (Ludvik 2004). There was no statistically significant change between the sweet potato intervention and the placebo (Analysis 1.5). Two trials reported data on BMI (Ludvik 2002; Ludvik 2008). Similarly, no statistically significant change in BMI was found in either of these trials of short-term (Ludvik 2002) and longer term (Ludvik 2008), treatment (Analysis 1.6).

Lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides)

All three trials provided data on total cholesterol and triglycerides. Both Ludvik 2002 and Ludvik 2008 provided data on HDL- and LDL-cholesterol. Compared with participants on placebos, those on 4 g/day sweet potato tablets demonstrated no statistically significant changes in either total cholesterol or triglyceride levels at three to five months (Analysis 1.7; Analysis 1.8).

There were also no statistically significant changes between the sweet potato tablets intervention and placebo groups for both LDL- and HDL-cholesterol levels (Analysis 1.9; Analysis 1.10).

Death from any cause, functional outcomes, health-related quality of life, well-being and costs

None of the publications assessed death from any cause, functional outcomes, health-related quality of life, well being or costs.

Timing of outcome measurements

One study reported outcomes at a one month interval between measurements of endpoints (Ludvik 2004). The other two studies reported outcomes measured at the end of study (Ludvik 2002; Ludvik 2008).

Subgroup analysis

We did not perform subgroup analyses due to the small number of included studies.

Sensitivity analyses

We did not perform sensitivity analyses due to the small number of included studies.

Publication and small study bias

Drawing of funnel plots was not possible due to the small number of included studies.

DISCUSSION

The aim of this review was to assess the effects of sweet potato (*Ipomoea batatas*) for type 2 diabetes mellitus (T2DM).

Summary of main results

We included three trials with 140 participants who had T2DM. The findings are presented in the Summary of findings for the main comparison. The mean duration of treatment was 3.2

months. The trials included in this review measured surrogate outcomes and evaluated adverse events (Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11). Compared with placebo, the sweet potato tablets did not show any significant improvement in blood glucose control in terms of normalisation, or a reduction in fasting blood glucose with a low dose of 2 g/day for six weeks. However, there was a statistically significant improvement in fasting blood glucose and glycosylated haemoglobin A1c (HbA1c) with an increased dose of 4 g/day of sweet potato tablets (Analysis 1.1; Analysis 1.3). There was no documentation of serious adverse events or adverse events due to participants dropping-out of the trials. There were suggestions of improved insulin sensitivity (Appendix 13). There were also no statistically significant changes in body weight, body mass index or lipid profiles.

However, one needs to exercise caution when interpreting these findings. Generally, the effect estimates were small. In addition to the low methodological quality of the publications, there were no data provided on diabetic complications and morbidity, functional outcomes, health-related quality of life, well-being, death from any cause or costs.

Overall completeness and applicability of evidence

All three trials selected for this review were conducted by the same author and used similar proprietary sweet potato (Caiapo) preparations in the interventions. No details of the type of placebos used were reported. Furthermore, the time points for assessment of the effects of intervention for the three trials differed. These time points ranged from six weeks (Ludvik 2002), to five months (Ludvik 2004; Ludvik 2008). No data on outcomes were available beyond five months. There were also no relevant data for identical time points that could be extracted from these publications. Therefore, at present there are insufficient data to assess adequately the benefit: risk ratio of sweet potato for T2DM.

Quality of the evidence

All three trials had an unclear risk of bias in at least two domains (selection and performance biases). There was insufficient information about randomisation and blinding methods. Most of the pre-specified outcomes were objectively measured and were reported. The main limitations were the lack of information on the implementation of the randomisation and blinding processes. Furthermore, the small sample size and number of events in each trial were affected by greater sampling variation, which is reflected in the large confidence intervals of the effect estimates.

Potential biases in the review process

There are several limitations with this systematic review: firstly, the small number of trials published. Furthermore, all these trials showed findings of beneficial effects of the specific sweet potato preparation on glucose metabolism. Apart from possible publication bias, other biases may have occurred during the selection of participants, administration of treatment, and assessment of outcomes. Therefore, inadequate reporting of the processes of randomisation and blinding may be associated with exaggerated effects of the interventions. Moreover, less methodologically-rigorous trials tend to show significantly larger intervention effects than more rigorous trials (Egger 2003; Kjaergard 2001; Moher 1998; Schulz 1995).

Secondly, the small sample size of the trials, which leads to diminished power of the results, may explain the small differences in effect estimate between the interventions and placebo. In other words, due to the size of these trials, the analyses may not establish with confidence that the two interventions have equivalent effects (Piaggio 2001; Pocock 1991). Thirdly, all the trials reported end-of-treatment values that ranged from six weeks to five months, and long-term responses beyond this period are not known. Fourthly, there were insufficient data about adverse events from two trials (Ludvik 2004; Ludvik 2008). As a result, the incidence of adverse events cannot be differentiated clearly between the sweet potato intervention and placebo. Fifthly, similar sweet potato preparations were used in the intervention arms and the efficacy of other sweet potato nutraceuticals is not known. Finally, although none of the trials provided information on ethnicity of the participants, the recruitment of participants was limited to the European population. Thus, the validity and applicability of the results to other ethnic groups or populations is not known.

Agreements and disagreements with other studies or reviews

Previous reviews focused on experimental studies of animal models and the use of sweet potato in promoting health in humans. There has been no systematic review of the effects of sweet potato on T2DM. This review included three available RCTs. The relatively small sample and effect estimates unfortunately do not provide sufficient evidence for any reliable conclusion of the potential benefits or harmful effects of sweet potato for T2DM.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence about the use of sweet potato for type 2 diabetes mellitus (T2DM).

Implications for research

Although there is reasonable evidence from animal models and clinical trials, including randomised controlled trials (RCTs), for suggesting that the sweet potato nutraceuticals may help in the management of T2DM, there are methodological issues: only one type of tablet derived from the tuber of a specific variety of sweet potato was tested in these RCTs. The results of the trials were from a predominantly European population and of relatively short duration (five months or less). Furthermore, these trials had a low power due to small sample sizes. RCTs with sample sizes that provide adequate power, of longer duration and in different T2DM populations would be useful to assess the efficacy of this nutraceutical further. The methods for detecting and monitoring, as well as the clarity of reporting of adverse effects also need to be scrutinised.

There are many other varieties of sweet potato. In addition to the tuber, other parts of the plants may be useful in glycaemic control. However, the complex issues surrounding differences and contaminants from growing, harvesting and processing the plant, as well as climatic variations may affect the characterisation as well as the production of reliable and consistently effective products (WHO 2007). In turn, this may undermine the therapeutic usefulness of products derived from this plant in glycaemic control in mainstream medicine. In addition to teasing out these issues, cost-benefit evaluation may also be useful.

Research into the effects of sweet potato on long-term complications of T2DM in humans is still unavailable. The presence of confounders, variations in the diet, as well as the difficulty in recording dietary intake over a long period make it difficult to interpret these complications when present.

The contribution of the highly nutritious sweet potato plant to the health of the healthy population is well-recognised. However, the effects of sweet potato in the diet of people with T2DM need to be evaluated, particularly in parts of the world where it is common to use many varieties of this vegetable. For reliable conclusions, observational trials and RCTs of short-, intermediate- and long-term use need to be large and of rigorous quality.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ludvik 2002

Methods	Parallel RCT Randomisation ratio: 1:1 Superiority design
Participants	**Inclusion criteria:** clinically stable T2DM on diet only **Exclusion criteria:** no information **Diagnostic criteria:** authors' criteria
Interventions	**Number of study centres:** no information **Treatment before study:** diabetic diet **Titration period:** nil **Experimental intervention groups:** 1. Tablets each containing 168 mg powdered white-skinned sweet potato (*Ipomoea batatas*)

Ludvik 2002 *(Continued)*

	2. Tablets each containing 336 mg powdered white-skinned sweet potato (*Ipomoea batatas* Participants in each group received 4 tablets 3 times daily after meals for a period of 6 weeks. A total of 2 g and 4 g/day were ingested by participants in each group, respectively **Control intervention:** Placebo tablets. No information on the contents of these tablets All patients were on diet regimen during the study
Outcomes	**Outcomes reported in abstract of publication:** **Primary outcome(s):** (as stated in the publication) change in fasting blood glucose **Seondary outcome(s):** (as stated in the publication) change in plasma insulin level, serum cholesterol and weight **Additional outcome(s):** incidence of adverse events
Study details	**Run-in period:** no information **Was s tudy terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication:** English **Commercial funding:** grant from manufacturer **Publication status:** peer review journal
Stated aim of study	Quote from publication: "To assess the effect of caiapo on glucose metabolism, its tolerability and mode of action in male Caucasian type 2 diabetic patients".
Notes	Letter to editor. Pilot study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "randomised to receive placebo or 2 (low dose) or 4 g (high dose) caiapo" Comment: there was no description of generation of the random sequence; furthermore, reports of 2 other trials by the same principal investigators that used a similar intervention also provided no information about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: there was no information provided about the method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote from publication: "double-blind" Comment: there was no other information available concerning blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: fasting blood glucose was specifically accessed at each visit for each participant
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants completed the study, no treatment withdrawals or major adverse events reported

Ludvik 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: primary outcomes were stated
Other bias	Unclear risk	Comment: there was no information about the sample size calculation or exclusion criteria; there was also insufficient information to assess other important risks of bias

Ludvik 2004

Methods	Parallel RCT Randomisation ratio: 1:1 Superiority design
Participants	**Inclusion criteria:** clinically stable T2DM on diet only **Exclusion criteria:** renal, hepatic, cardiovascular, hematological, respiratory, autoimmune, neurological diseases or other endocrine dysfunction that could interfere with the study **Diagnostic criteria:** authors' criteria
Interventions	**Number of study centres:** no information **Treatment before study:** oral hypoglycaemic agents withdrawn 2 weeks before trial **Titration period:** nil **Intervention group:** 4 g of Caiopo (*Ipomoea batatas*) once daily **Control intervention:** Placebo tablets; no information provided regarding the content of these tablets All participants were on diet regimen during the study
Outcomes	**Outcomes reported in abstract of publication:** **Primary outcome(s):** (as stated in the publication) change in fasting blood glucose and 2-hour postprandial blood glucose; change in HbA1c **Seondary outcome(s):** (as stated in the publication) change in cholesterol and triglyceride levels **Additional outcome(s):** incidence of adverse events
Study details	**Run-in period:** 5 participants on antidiabetic medication (metformin and/or glibenclamide) had their medications withdrawn 2 weeks before the start of the study **Was s tudy terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication:** English **Commercial funding:** grant from manufacturer **Non-commercial funding:** nil **Publication status:** peer review journal

Ludvik 2004 *(Continued)*

Stated aim of study	Quote from publication: "... assessment of the efficacy and tolerability of Caiapo (4 g/day) compared with placebo when administered for 12 consecutive weeks for type 2 diabetic patients ..."
Notes	Original research journal article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "randomly divided into two groups" Comment: the process of randomisation was not specified
Allocation concealment (selection bias)	Unclear risk	Comment: there was no information about the adequacy of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote from publication: "double-blind" Comment: there was no other information available about blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: fasting blood glucose and HbA1c were specifically measured
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants completed the study, no treatment withdrawals or major adverse events reported
Selective reporting (reporting bias)	Low risk	Comment: primary outcome measures were stated
Other bias	Low risk	Comment: none detected

Ludvik 2008

Methods	Parallel RCT Randomisation ratio: 1:1 Superiority design
Participants	**Inclusion criteria:** clinically stable T2DM on diet only **Exclusion criteria:** no information **Diagnostic criteria:** authors' criteria
Interventions	**Number of study centres:** multiple centres (no information on exact number) **Treatment before study:** no hypoglycaemic drugs 4 weeks prior to baseline visit **Titration period:** nil **Intervention group:** 4 g of Caiopo (*Ipomoea batatas*) once daily **Control intervention:**

Ludvik 2008 *(Continued)*

	Placebo tablets; no information provided about the content of these tablets All participants were on diet regimen during the study
Outcomes	**Outcomes reported in abstract of publication:** **Primary outcome(s):** (as stated in the publication) change in fasting blood glucose and 2-hour post-prandial blood glucose; change in HbA1c **Seondary outcome(s):** (as stated in the publication) change in cholesterol and triglyceride levels **Additional outcome(s):** incidence of adverse events
Study details	**Run-in period:** medications that affect blood glucose levels such as corticosteroids, high-dose diuretics or beta-blockers were stopped during the 2 weeks prior to screening and for the duration of the study; screening for participants took place 1 month prior to start of study; hypoglycaemic drugs were withdrawn 4 weeks before the start of the study **Was s tudy terminated early (for benefit/because of adverse events):** no
Publication details	**Language of publication:** English **Commercial other funding:** grant from manufacturer **Non-commercial funding:** nil **Publication status:** peer review journal
Stated aim of study	Quote from publication: "To further evaluate the mode of action of Caiapo on insulin sensitivity over an extended period of time as well as the effects on fibrinogen and other markers of low-grade inflammation".
Notes	Original research journal article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "randomised" Comment: there was no information provided about the process used to generate the random sequence
Allocation concealment (selection bias)	Unclear risk	Comment: there was no information provided about the adequacy of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote from publication: "double-blind" Comment: there was no other information available about blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the primary and secondary outcomes were measured objectively
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote from publication: "27/88 patients dropped out (due to pregnancy (1) and non-compliance to follow-up visits)" Comment: there was no information about the number of participants who dropped out of the intervention and the control groups

Ludvik 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: important primary and secondary outcomes were adequately reported
Other bias	Low risk	Comment: none detected

RCT: randomised controlled trial; T2DM: type 2 diabetes mellitus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ludvik 2003	The objective was evaluation of the mechanism of action of *Ipomoea batatas* and not the effects of the intervention on T2DM. This paper did not contain relevant outcome data for assessment

T2DM: type 2 diabetes mellitus

DATA AND ANALYSES

Comparison 1. Sweet potato (Caiapo) tablets versus placebo

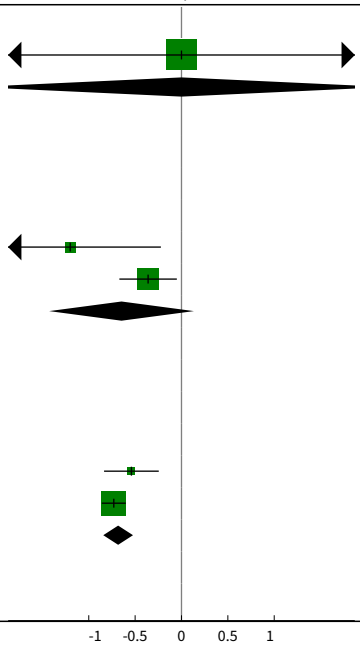
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fasting blood glucose (final values)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Sweet potato (2 g/day) at 6 weeks	1	12	Mean Difference (IV, Random, 95% CI)	0.0 [-2.23, 2.23]
1.2 Sweet potato (4 g/day) at 6 weeks and below 3 months	2	73	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.43, 0.13]
1.3 Sweet potato (4 g/day) at 3 to 5 months	2	122	Mean Difference (IV, Random, 95% CI)	-0.68 [-0.84, -0.52]
2 Postprandial blood glucose (final values)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Sweet potato (4 g/day) at less than 3 months	1	61	Mean Difference (IV, Random, 95% CI)	-0.98 [-2.07, 0.11]
2.2 Sweet potato (4 g/day) at 3 months	1	61	Mean Difference (IV, Random, 95% CI)	-1.01 [-2.19, 0.17]
3 HbA1c (final values)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Sweet potato (4 g/day) at 3 to 5 months	2	122	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.57, -0.04]
4 Fasting plasma insulin (final values)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Sweet potato tablets (2 g/day) at 6 weeks	1	12	Mean Difference (IV, Random, 95% CI)	0.30 [-3.94, 4.54]
4.2 Sweet potato tablets (4 g/day) at 6 weeks	1	12	Mean Difference (IV, Random, 95% CI)	4.5 [-0.93, 9.93]
4.3 Sweet potato tablets (4 g/day) at 5 months	1	61	Mean Difference (IV, Random, 95% CI)	1.11 [-1.85, 4.07]
5 Body weight (final values)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Sweet potato (4 g/day) at 3 months	1	61	Mean Difference (IV, Random, 95% CI)	-1.0 [-5.32, 3.32]
6 BMI (final values)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Sweet potato (4 g/day) at 6 weeks	1	12	Mean Difference (IV, Random, 95% CI)	-1.10 [-4.43, 2.23]
6.2 Sweet potato (4 g/day) at 5 months	1	61	Mean Difference (IV, Random, 95% CI)	1.0 [-0.81, 2.81]
7 Total cholesterol (final values)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Sweet potato (4 g/day) at 3 to 5 months	2	122	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.10, 0.16]
8 Triglycerides (final values)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Sweet potato (4 g/day) at 3 to 5 months	2	122	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.41, 0.35]
9 HDL-cholesterol (final values)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Sweet potato (2 g/day) at 6 weeks	1	12	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.63, 0.11]
9.2 Sweet potato (4 g/day) at 6 weeks	1	12	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.64, 0.02]
9.3 Sweet potato (4 g/day) at 5 months	1	61	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.31, 0.03]
10 LDL-cholesterol (final values)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Sweet potato (2 g/day) at 6 weeks	1	12	Mean Difference (IV, Random, 95% CI)	0.02 [-0.95, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Sweet potato (4 g/day) at 6 weeks	1	12	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.92, -0.20]
10.3 Sweet potato (4 g/day) at 5 months	1	61	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.60, 0.34]

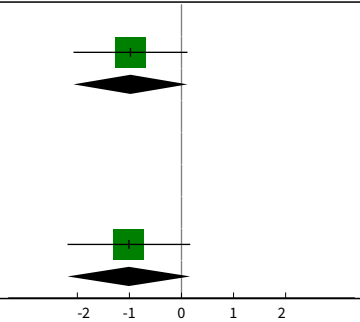
Analysis 1.1. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 1 Fasting blood glucose (final values).

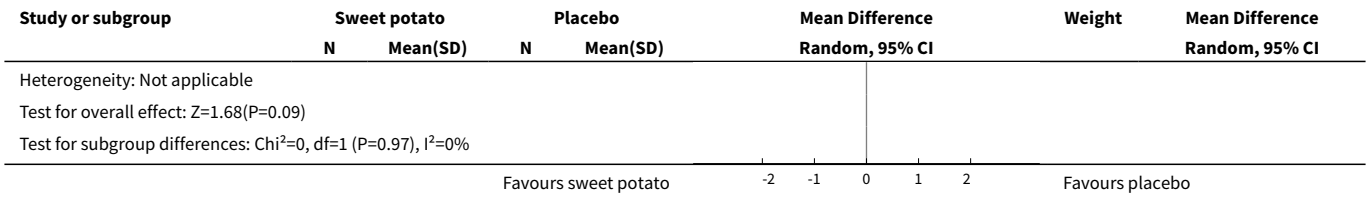
Study or subgroup	Sweet potato N	Sweet potato Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 Sweet potato (2 g/day) at 6 weeks							
Ludvik 2002	6	8.4 (2.7)	6	8.4 (0.7)		100%	0[-2.23,2.23]
Subtotal ***	**6**		**6**			**100%**	**0[-2.23,2.23]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.1.2 Sweet potato (4 g/day) at 6 weeks and below 3 months							
Ludvik 2002	6	7.2 (1)	6	8.4 (0.7)		34.14%	-1.2[-2.18,-0.22]
Ludvik 2004	30	7.3 (0.6)	31	7.7 (0.7)		65.86%	-0.36[-0.67,-0.05]
Subtotal ***	**36**		**37**			**100%**	**-0.65[-1.43,0.13]**
Heterogeneity: Tau^2=0.22; Chi^2=2.58, df=1(P=0.11); I^2=61.18%							
Test for overall effect: Z=1.62(P=0.1)							
1.1.3 Sweet potato (4 g/day) at 3 to 5 months							
Ludvik 2004	30	7.1 (0.5)	31	7.7 (0.7)		24.63%	-0.54[-0.83,-0.25]
Ludvik 2008	27	7.1 (0.3)	34	7.8 (0.2)		75.37%	-0.73[-0.86,-0.6]
Subtotal ***	**57**		**65**			**100%**	**-0.68[-0.84,-0.52]**
Heterogeneity: Tau^2=0; Chi^2=1.34, df=1(P=0.25); I^2=25.29%							
Test for overall effect: Z=8.35(P<0.0001)							



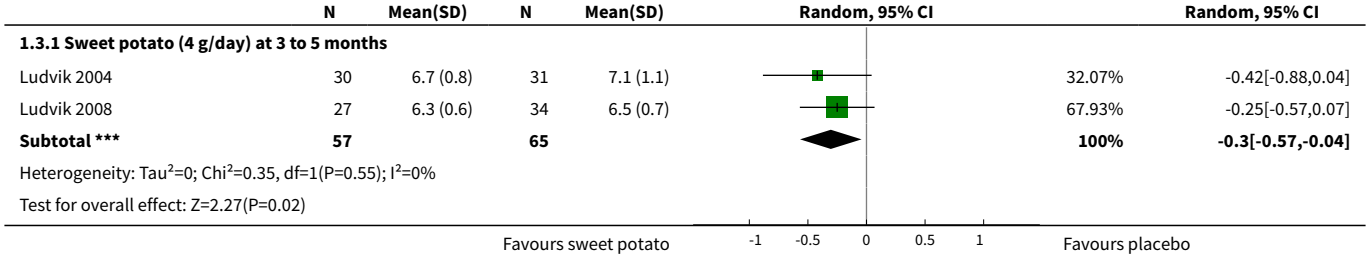
Analysis 1.2. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 2 Postprandial blood glucose (final values).

Study or subgroup	Sweet potato N	Sweet potato Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 Sweet potato (4 g/day) at less than 3 months							
Ludvik 2004	30	9.4 (2.1)	31	10.4 (2.3)		100%	-0.98[-2.07,0.11]
Subtotal ***	**30**		**31**			**100%**	**-0.98[-2.07,0.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.76(P=0.08)							
1.2.2 Sweet potato (4 g/day) at 3 months							
Ludvik 2004	30	9 (2.5)	31	10.1 (2.2)		100%	-1.01[-2.19,0.17]
Subtotal ***	**30**		**31**			**100%**	**-1.01[-2.19,0.17]**

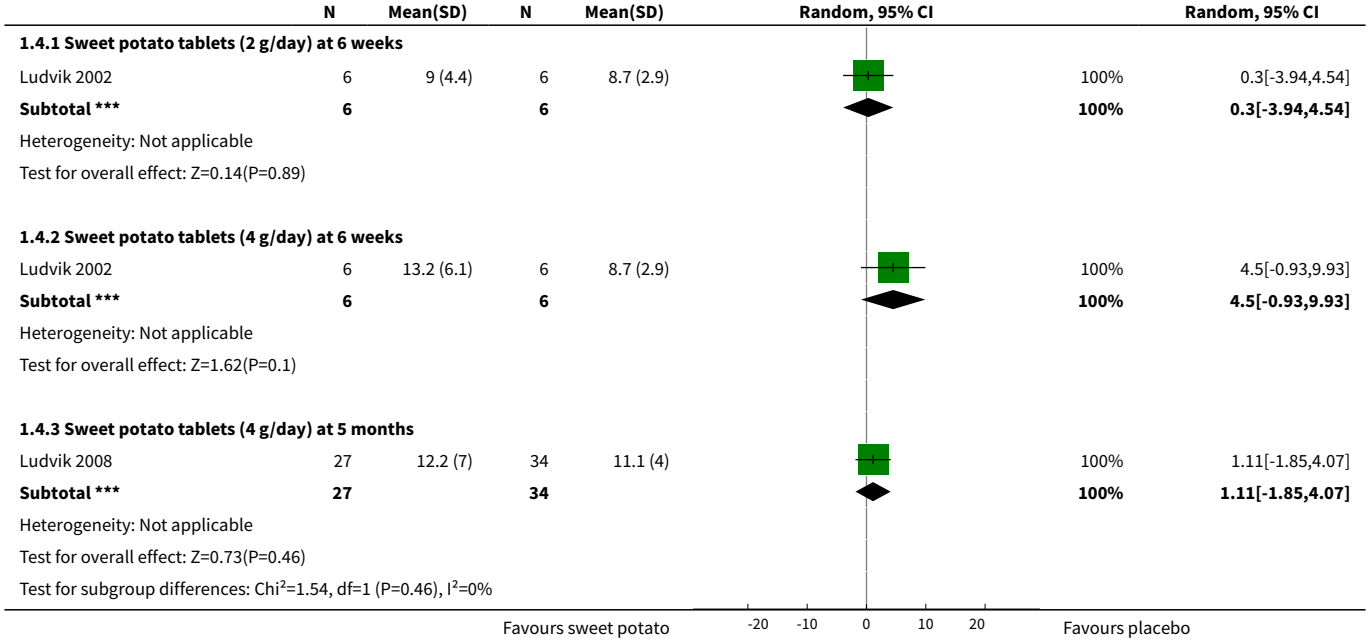




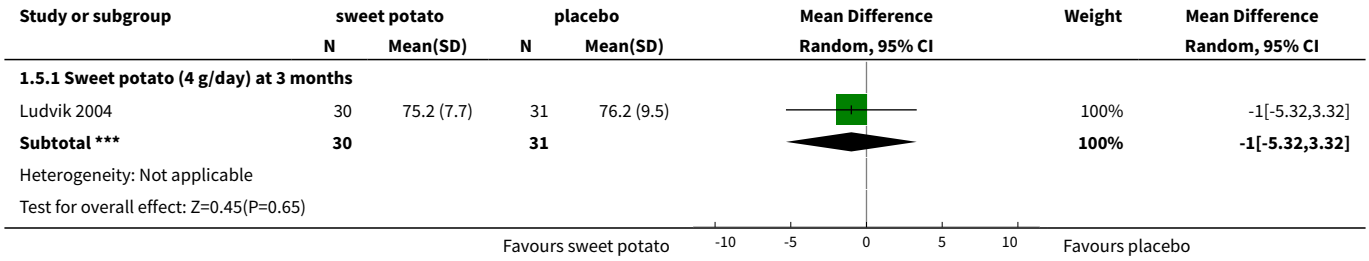
Analysis 1.3. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 3 HbA1c (final values).



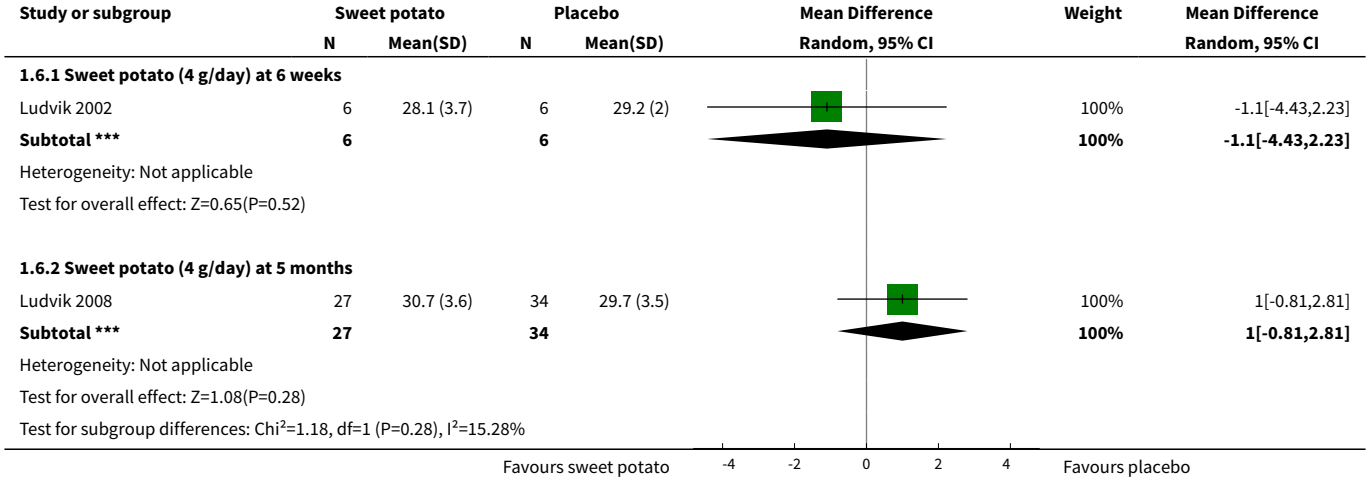
Analysis 1.4. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 4 Fasting plasma insulin (final values).



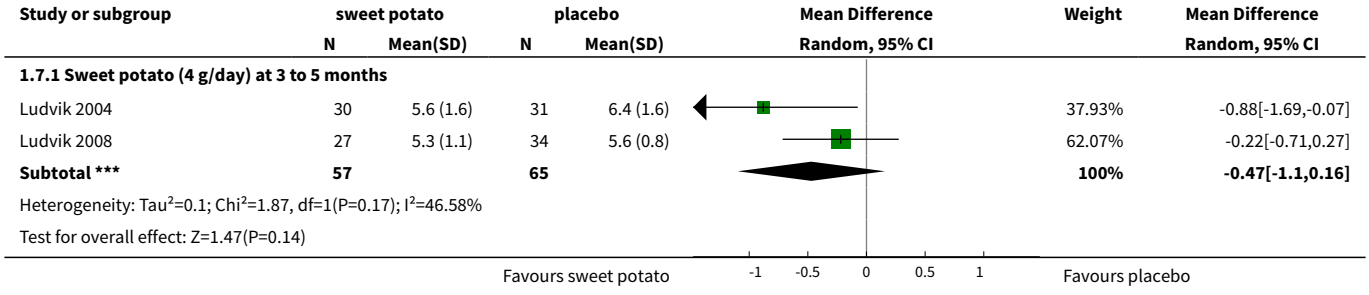
Analysis 1.5. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 5 Body weight (final values).



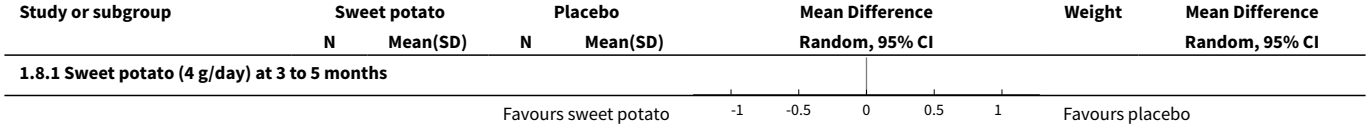
Analysis 1.6. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 6 BMI (final values).

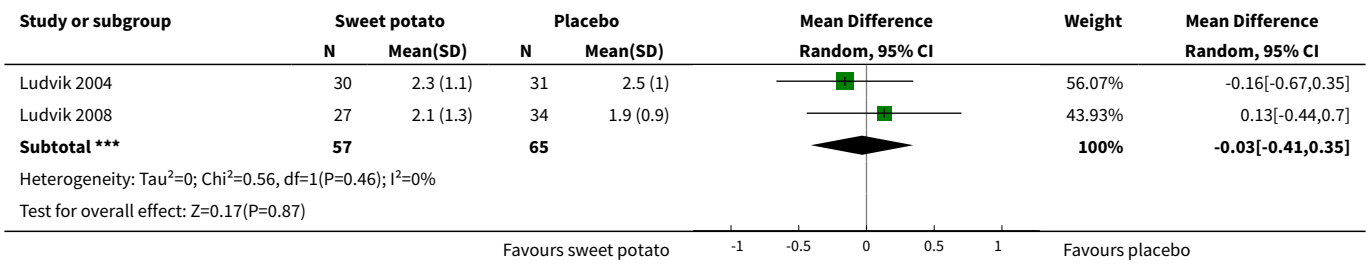


Analysis 1.7. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 7 Total cholesterol (final values).

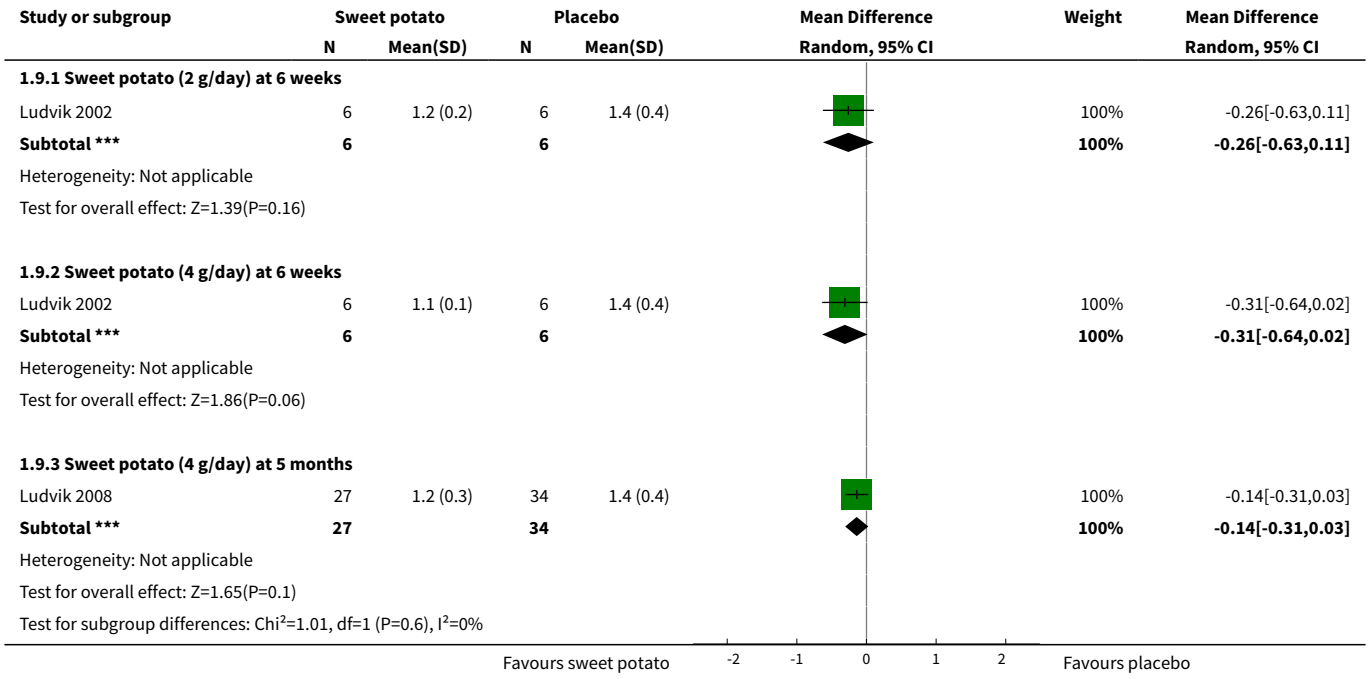


Analysis 1.8. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 8 Triglycerides (final values).

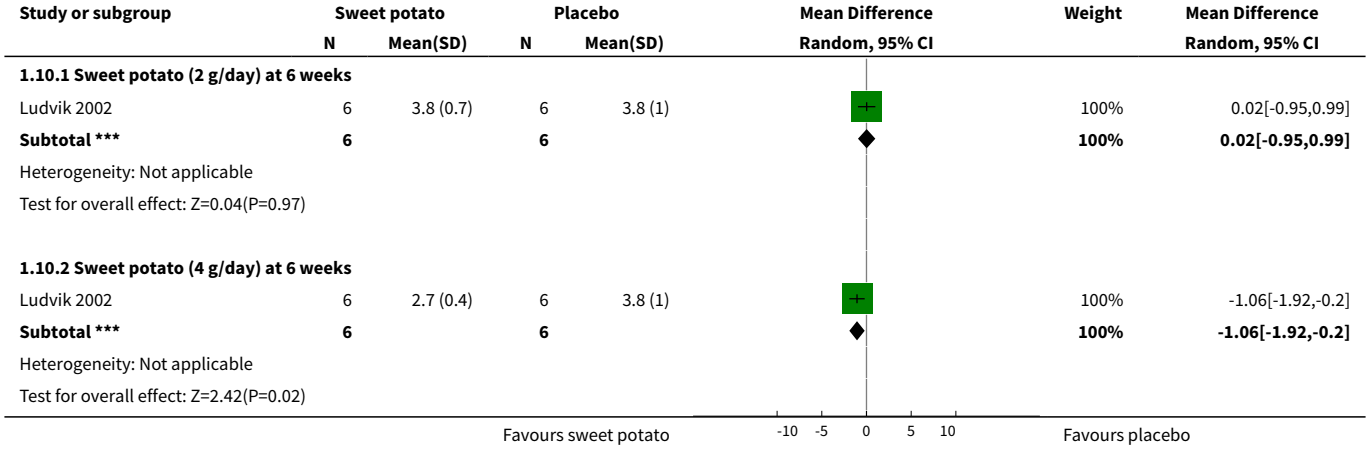




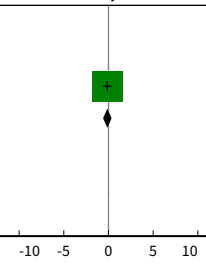
Analysis 1.9. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 9 HDL-cholesterol (final values).



Analysis 1.10. Comparison 1 Sweet potato (Caiapo) tablets versus placebo, Outcome 10 LDL-cholesterol (final values).



Study or subgroup	Sweet potato N	Sweet potato Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.10.3 Sweet potato (4 g/day) at 5 months							
Ludvik 2008	27	3.2 (1)	34	3.4 (0.9)		100%	-0.13[-0.6,0.34]
Subtotal ***	**27**		**34**			**100%**	**-0.13[-0.6,0.34]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.54(P=0.59)							
Test for subgroup differences: Chi^2=3.92, df=1 (P=0.14), I^2=48.92%							



ADDITIONAL TABLES

Table 1. Overview of study populations

Characteristic	Intervention(s) and comparator(s)	Sample size	[N] Screened/ eligible	[N] Randomised	[N] Safety	[N] ITT	[N] Finishing study	[%] Randomised finishing study	Follow-up[a]
Ludvik 2002	I1: 2 g powdered white-skinned sweet potato (*Ipomoea batatas*) tablet	-	-	6	6	-	6	100	6 weeks
	I2: 4 g powdered white-skinned sweet potato (*Ipomoea batatas*) tablet			6	6		6	100	
	C: Placebo			6	6		6	100	
	Total:			18	18		18	100	
Ludvik 2004	I: 4 g of Caiopo (*Ipomoea batatas*) tablet	-	-	30	30	-	30	100	3 months
	C: Placebo			31	31		31	100	
	Total:			61	61		61	100	
Ludvik 2008	I: 4 g of Caiopo (*Ipomoea batatas*) tablet	21	-	-	-	-	27	N/A	5 months
	C Placebo	21		-	-		34	N/A	
	Total:	42	88		-		61	69.3	
Grand total	***All interventions***			***I1: 63 + ? I2: 6***			***I1: 63 I2: 6***		
	All c omparators			***71 + ?***			***71***		
	All interventions and c omparators			***140 + ?***			***140***		

[a]Duration of intervention and/or follow-up under randomised conditions until end of study

"-" denotes not reported
"+ ?" denotes number of unreported participants who took part in the study
C: comparator; I: intervention; ITT: intention-to-treat; N/A: not applicable

APPENDICES

Appendix 1. Search strategies

Search terms and databases
Unless otherwise stated, search terms are free text terms '$': stands for any character; '?': substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp: exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word.

The Cochrane Library

#1 MeSH descriptor Diabetes mellitus, type 2 explode all trees
#2 MeSH descriptor Insulin resistance explode all trees
#3 ((impaired in All Text and glucose in All Text and toleranc* in All Text) or (glucose in All Text and intoleranc* in All Text) or (insulin* in All Text and resistanc* in All Text))
#4 (obes* in All Text near/6 diabet* in All Text)
#5 (MODY in All Text or NIDDM in All Text or TDM2 in All Text)
#6 ((non in All Text and insulin* in All Text and depend* in All Text) or (noninsulin* in All Text and depend* in All Text) or (non in All Text and insulindepend* in All Text) or noninsulindepend* in All Text)
#7 (typ* in All Text and (2 in All Text near/6 diabet* in All Text))
#8 (typ* in All Text and (II in All Text near/6 diabet* in All Text))
#9 (non in All Text and (keto* in All Text near/6 diabet* in All Text))
#10 (nonketo* in All Text near/6 diabet* in All Text)
#11 (adult* in All Text near/6 diabet* in All Text)
#12 (matur* in All Text near/6 diabet* in All Text)
#13 (late in All Text near/6 diabet* in All Text)
#14 (slow in All Text near/6 diabet* in All Text)
#15 (stabl* in All Text near/6 diabet* in All Text)
#16 (insulin* in All Text and (defic* in All Text near/6 diabet* in All Text))
#17 (plurimetabolic in All Text and syndrom* in All Text)
#18 (pluri in All Text and metabolic in All Text and syndrom* in All Text)
#19 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#20 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#21 (#19 or #20)
#22 MeSH descriptor Diabetes insipidus explode all trees
#23 (diabet* in All Text and insipidus in All Text)
#24 (#22 or #23)
#25 (#21 and not #24)
#26 MeSH descriptor Ipomoea batatas explode all trees
#27 MeSH descriptor Convolvulaceae explode all trees
#28 Convolvulaceae in All Text
#29 ((sweet in All Text and potato in All Text)
#30 (ipomoea in All Text and batatas in All Text)
#31 (#26 or #27 or #28 or #29 or #30)
#32 (#25 and #31)

MEDLINE

1. ipomoea batatas.mp.
2. sweet potato.mp.
3. Convolvulaceae.mp.
4. or/1-3
5. exp Diabetes Mellitus, Type 2/
6. exp Insulin Resistance/
7. exp Glucose Intolerance/
8. (impaired glucos$ toleranc$ or glucos$ intoleranc$ or insulin resistan$).tw,ot.

(Continued)

9. (obes$ adj3 diabet$).tw,ot.
10. (MODY or NIDDM or T2DM).tw,ot.
11. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or noninsulin?depend$).tw,ot.
12. ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet$).tw,ot.
13. ((keto?resist$ or non?keto$) adj6 diabet$).tw,ot.
14. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).tw,ot.
15. or/5-14
16. exp Diabetes Insipidus/
17. diabet$ insipidus.tw,ot.
18. 16 or 17
19. 15 not 17
20. 4 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomi?ed.ab.
24. placebo.ab.
25. drug therapy.fs.
26. randomly.ab.
27. trial.ab.
28. groups.ab.
29. or/21-28
30. Meta-analysis.pt.
31. exp Technology Assessment, Biomedical/
32. exp Meta-analysis/
33. exp Meta-analysis as topic/
34. hta.tw,ot.
35. (health technology adj6 assessment$).tw,ot.
36. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
37. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systemat$)).tw,ot.
38. or/30-37
39. (comment or editorial or historical-article).pt.
40. 38 not 39
41. 29 or 40
42. 20 and 41
43. (animals not (animals and humans)).sh.
44. 42 not 43

EMBASE

1. exp Ipomoea batatas extract/ or exp Ipomoea batatas/
2. sweet potato.tw,ot.
3. Convolvulaceae.tw,ot.
4. or/1-3
5. exp Diabetes Mellitus, Type 2/
6. exp Insulin Resistance/
7. (MODY or NIDDM or T2D or T2DM).tw,ot.
8. ((typ? 2 or typ? II or typ?II or typ?2) adj3 diabet*).tw,ot.
9. (obes* adj3 diabet*).tw,ot.
10. (non insulin* depend* or non insulin?depend* or noninsulin* depend* or noninsulin?depend*).tw,ot.
11. ((keto?resist* or non?keto*) adj3 diabet*).tw,ot.
12. ((adult* or matur* or late or slow or stabl*) adj3 diabet*).tw,ot.
13. (insulin* defic* adj3 relativ*).tw,ot.
14. insulin* resistanc*.tw,ot.
15. or/5-14
16. exp Diabetes Insipidus/
17. diabet* insipidus.tw,ot.
18. 16 or 17
19. 15 not 18
20. 4 and 19

(Continued)

21. exp Randomized Controlled Trial/
22. exp Controlled Clinical Trial/
23. exp Clinical Trial/
24. exp Comparative Study/
25. exp Drug comparison/
26. exp Randomization/
27. exp Crossover procedure/
28. exp Double blind procedure/
29. exp Single blind procedure/
30. exp Placebo/
31. exp Prospective Study/
32. ((clinical or control$ or comparativ$ or placebo$ or prospectiv$ or randomi?ed) adj3 (trial$ or stud$)).ab,ti.
33. (random$ adj6 (allocat$ or assign$ or basis or order$)).ab,ti.
34. ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ab,ti.
35. (cross over or crossover).ab,ti.
36. or/21-35
37. exp meta analysis/
38. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
39. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systematic$)).ab,ti,ot.
40. exp Literature/
41. exp Biomedical Technology Assessment/
42. hta.tw,ot.
43. (health technology adj6 assessment$).tw,ot.
44. or/37-43
45. (comment or editorial or historical-article).pt.
46. 44 not 45
47. 36 or 46
48. 20 and 47
49. limit 48 to human

'My NCBI' alert service

("ipomoea batatas"[MeSH Terms] OR ("ipomoea"[All Fields] AND "batatas"[All Fields]) OR "ipomoea batatas"[All Fields] OR ("sweet"[All Fields] AND "potato"[All Fields]) OR "sweet potato"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields])

CINAHL

1. MM "sweet potato"
2. MM "ipomoea batatas"
3. MM "Convolvulaceae"
4. #1 or #2 or #3
5. MM "insulin resistance"
6. MM "Diabetes Mellitus, Non-Insulin-Dependent"
7. TX Diabetes Complications
8. TX MODY or NIDDM or T2DM
9. TX non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend
10. TX diabet* N3 (typ* 2 or typ* II)
11. TX diabet* N6 (keto*resist* or non*keto*
12. TI (onset N3 (late or adult* or matur* or slow or stabl*)) and TI diabet*
13. AB (onset N3 (late or adult* or matur* or slow or stabl*)) and AB diabet*
14. TI (insulin* defic* or relativ*)
15. AB (insulin* defic* or relativ*)
16. TI (insulin* resistanc*)
17. AB (insulin* resistanc*)
18. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
19. MM "Diabetes Insipidus"
20. TX diabet* insipidus

(Continued)

21. # 19 or #20
22. #18 NOT #21
23. #4 and #22
24. TX Meta-analysis
25. TX Technology Assessment, Biomedical
26. #24 or #25
27. TX comment or editorial or historical-article
28. #26 NOT #27
29. AB randomized controlled trial
30. AB controlled clinical trial
31. AB cross over OR crossover
32. TX random* OR blind* OR placebo* OR group*
33. TX animal* NOT (animal* AND human*)
34. #29 or #30 or #31 or #32
35. #34 NOT #33
36. #28 or #35
37. #23 and #36

LILACS

1. (sweet potato or ipomoea batatas or Convolvulaceae) [Subject descriptor] and
2. (Diabetes mellitus or insulin resistance) [Palavras] and
3. (random$ or placebo$ or trial or group$) [Palavras]

Natural medicines comprehensive database

1. sweet potato, diabetes
2. ipomoea batatas, diabetes
3. Convolvulaceae, diabetes

OpenGrey

1. (sweet potato or ipomoea batatas or Convolvulaceae) [Abstract] and
2. (Diabetes mellitus or insulin resistance) [Abstract] and
3. (random or placebo or trial or group) [Abstract]

Natural Medicines Comprehensive Databas

1. sweet potato, diabetes
2. ipomoea batatas, diabetes
3. Convolvulaceae, diabetes

Proquest Dissertations and Theses database

1. ("sweet potato") OR (“sweet potato”) OR ("convolvulaceae") Citation and document text
2. ("typ* 2") OR ("typ* II") OR ("late") OR ("maturity") OR ("n???insulin") AND ("diabet*") Citation and document text
3. (NIDDM*) OR (MODY*) OR (TIIDM) OR (T2DM) Citation and document text
4. ((("typ* 2") OR ("typ* II") OR ("late") OR ("maturity") OR ("n???insulin") AND ("diabet*")) OR ((NIDDM*) OR (MODY*) OR (TIIDM) OR (T2DM))) AND ((("sweet potato") OR (“sweet potato”) OR ("convolvulaceae"))) Citation and document text

Appendix 2. Description of interventions

Characteristic	Intervention(s) [route, frequency, total dose/day]	Comparator(s) [route, frequency, total dose/day]
Ludvik 2002	I1: sweet potato (Caiapo) tablets: oral; 2 g 3 times/day	C: placebo; oral; 3 times/day

(Continued)

	I2: sweet potato (Caiapo) tablets: oral; 4 g 3 times/day	
Ludvik 2004	I: sweet potato (Caiapo) tablets: oral; once daily; 4 g/day	C: placebo; oral; 3 times/day
Ludvik 2008	I: sweet potato (Caiapo) tablets: oral; once daily; 4 g/day	C: placebo; oral; 3 times/day

Footnotes

C: comparator; I: intervention

Appendix 3. Baseline characteristics (I)

Characteristic	Intervention(s) and comparator(s) [dosage per day]	Duration of intervention (duration of follow-up)	Participating population	Study period [year to year]	Country	Setting	Duration of diabetes [mean years (SD)]
Ludvik 2002	I1: sweet potato (Caiapo) tablets 2 g	6 weeks (6 weeks)	Male participants with T2DM on diet	-	Austria	-	-
	I2: sweet potato (Caiapo) tablets 4 g	6 weeks (6 weeks)					
	C: placebo	6 weeks (6 weeks)					
Ludvik 2004	I: sweet potato (Caiapo) tablets 4 g	3 months (3 months)	People with T2DM on diet	-	Switzerland	Outpatients (offices of general practitioners)	-
	C: placebo	3 months (3 months)					
Ludvik 2008	I: sweet potato (Caiapo) tablets 4 g	5 months (5 months)	People with T2DM	-	Austria and Germany	Outpatients clinics	3.5 (4.2)
	C: placebo	5 months (5 months)					4.2 (2.9)

Footnotes

"-" denotes not reported

C: comparator; I: intervention; SD: standard deviation; T2DM: type 2 diabetes mellitus

Appendix 4. Baseline characteristics (II)

Characteristic	Intervention(s) and comparator(s)	Sex [female %]	Age [mean years (SD)]	HbA1c [%]	BMI [mean kg/m^2 (SD)]	Co-medications/ co-interventions	Co-morbidities
Ludvik 2002	I1: sweet potato (Caiapo) tablets 2 g	0	-	7.3 (1.0)	25.5 (2.0)	-	-
	I2: sweet potato (Caiapo) tablets 4 g	0	-	7.1 (0.7)	28.6 (3.2)		
	C: placebo	0	-	7.0 (0.7)	28.9 (2.2)		
	All:	0	58 (8)		27.7 (11.5)		
Ludvik 2004	I: sweet potato (Caiapo) tablets 4 g	50	55.2 (2.1)	7.2 (0.8)	28.2 (2.2)	-	-
	C: placebo	38.7	55.6 (1.5)	7.0 (1)	27.6 (1.7)		
	All:	44.3	55.2 (16.4)				
Ludvik 2008	I: sweet potato (Caiapo) tablets 4 g	48.1	57.2 (9.35)	6.5 (0.6)	31.1 (3.7)	-	-
	C: placebo	47.1	61.1 (8.7)	6.3 (0.6)	29.9 (3.5)		
	All:	47.5	59.4 (10.2)				

Footnotes

"-" denotes not reported

C: comparator; I: intervention; SD: standard deviation

Appendix 5. Matrix of study endpoints (publications)

Characteristic		Endpoint reported in publication	Endpoint not reported in publication	Time of measurement[a]
Ludvik 2002	**Review's primary outcomes**			
	Gycaemic control	x		0, 1.5 months
	Morbidity		x	
	Adverse effects	x		0, 1.5 months
	Review's secondary outcomes			
	Serum insulin, C-peptide or insulin sensitivity		x	
	Body weight or BMI	x		0, 1.5 months
	Lipids (total, LDL- and HDL-cholesterol; triglycerides)	x		0, 1.5 months
	Health-related quality of life		x	
	Well-being		x	
	Physical and cognitive function		x	
	Costs		x	
	Other than review's primary/secondary outcomes reported in publication (classification: P/S/O)[b]			
	Blood pressure (S): 0, 1.5 mo			
	Subgroups reported in publication			
	-			
Ludvik 2004	**Review's primary outcomes**			
	Gycaemic control	x		0, 2, 3 mo
	Morbidity		x	
	Adverse effects	x		0, 2, 3 mo
	Review's secondary outcomes			
	Serum insulin, C-peptide or insulin sensitivity		x	
	Body weight or BMI	x		0, 2, 3 mo
	Lipids (total, LDL- and	x		0, 2, 3 mo

(Continued)

	HDL-cholesterol; triglycerides)		
	Health-related quality of life	x	
	Well-being	x	
	Physical and cognitive function	x	
	Costs	x	
	Outcomes other than review's primary/secondary outcomes reported in publication (classification: P/S/O)[b]		
	Blood pressure: 0, 2, 3 months		
	Subgroups reported in publication		
	-		
Ludvik 2008	**Review's primary outcomes**		
	Gycaemic control	x	0, 5 months
	Morbidity	x	
	Adverse effects	x	0, 5 months
	Review's secondary outcomes		
	Serum insulin, C-peptide or insulin sensitivity	x	0, 5 months
	Body weight or BMI	x	
	Lipids (total, LDL- and HDL-cholesterol; triglycerides)	x	0, 5 months
	Health-related quality of life	x	
	Well-being	x	
	Physical and cognitive function	x	
	Costs	x	
	Other than review's primary/secondary outcomes reported in publication (classification: P/S/O)[b]		
	Adiponectin, fibrinogen: 0, 5 months		
	Subgroups reported in publication		

Footnotes

[a]Underlined data denote times of measurement for primary and secondary review outcomes, if measured and reported in the results section of the publication (other times represent planned but not reported points in time)

(Continued)

[b](P) Primary or (S) secondary endpoint(s) refer to verbatim statements in the publication, (O) other endpoints relate to outcomes which were not specified as 'primary' or 'secondary' outcomes in the publication

BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; N/A: not applicable

Appendix 6. Matrix of study endpoints (protocol/trial documents)

Characteristic/ Study ID (trial identifier)	Endpoint	Time of measurement
Ludvik 2002	**Glycaemic control** (P)	0, 1.5 months
	Serum insulin, C-peptide or insulin sensitivity (S)	0, 1.5 months
	Serum cholesterol (S)	0, 1.5 months
	Weight (S)	0, 1.5 months
	Adverse events (O)	0, 1.5 months
Ludvik 2004	**Glycaemic control** (P)	0, 2, 3 months
	Serum cholesterol and triglyceride (S)	0, 2, 3 months
	Adverse events (O)	0, 2, 3 months
Ludvik 2008	**Glycaemic control** (P)	0, 5 months
	Serum cholesterol and triglyceride (S)	0, 5 months
	Adverse events (O)	0, 5 months

Footnotes

[a]Endpoint in bold/italic = review's primary/secondary outcome

[b](P) Primary or (S) secondary endpoint(s) refer to verbatim statements in the publication, (O) other endpoints relate to outcomes that were not specified as 'primary' or 'secondary' outcomes in the report

Appendix 7. Definition of endpoint measurement (I)

Characteristic	Glycaemic control	Morbidity	Severe / serious adverse events	Insulin sensitivity	Health-related quality of life	Well-being	Physical function	Cognitive function
Ludvik 2002	Change in fasting blood glucose and HbA1c	-	ND	ND	-	-	-	-
Ludvik 2004	Change in fasting blood glucose and HbA1c	-	ND	ND	-	-	-	-
Ludvik 2008	Changes in HbA1c	-	ND	Oral glucose insulin sensitivity (OGIS), as glucose clearance from oral glucose tolerance test	-	-	-	-

Footnotes

"-" denotes not reported

HbA1c: glycosylated haemoglobin A1c; ND: not defined

Appendix 8. Definition of endpoint measurement (II)

Characteristic Study ID	Mild hypoglycaemia	Moderate hypoglycaemia	Severe hypoglycaemia	Nocturnal hypoglycaemia
Ludvik 2002	ND	ND	ND	ND
Ludvik 2004	ND	ND	ND	ND
Ludvik 2008	ND	ND	ND	ND

Footnotes

ND: not defined

Appendix 9. Adverse events (I)

Characteristic	Intervention(s) and comparator(s)	Deaths [N]	Deaths [%]	All adverse events [N]	All adverse events [%]	Severe/serious adverse events [N]	Severe/serious adverse events [%]
Ludvik 2002	I1: sweet potato (Caiapo) tablets 2 g	0	0	"No adverse events have been reported by the patients"	-	-	-
	I2: sweet potato (Caiapo) tablets 4 g	0	0				
	C: placebo	0	0				
Ludvik 2004	I: sweet potato (Caiapo) tablets 4 g	0	0	16/30	53.3	-	-
	C: placebo	0	0	14/31	45.2	-	-
Ludvik 2008	I: sweet potato (Caiapo) tablets 4 g	0	0	-	-	-	-
	C: placebo	0	0	-	-	-	-

Footnotes

"-" denotes not reported

C: comparator; I: intervention

Appendix 10. Adverse events (II)

Characteristic	Intervention(s) and comparator(s)	Left study due to adverse events [N]	Left study due to adverse events [%]	Hospitalisation [N]	Hospitalisation [%]	Out-patient treatment [N]	Out-patient treatment [%]
Ludvik 2002	I1: sweet potato (Caiapo) tablets 2 g	0	0	-	-	-	-
	I2: sweet potato (Caiapo) tablets 4 g	0	0	-	-	-	-
	C: placebo	0	0	-	-	-	-
Ludvik 2004	I: sweet potato (Caiapo) tablets (4 g per day)	0	0	-	-	-	-
	C: placebo	0	0	-	-	-	-
Ludvik 2008	I: sweet potato (Caiapo) tablets (4 g per day)	0	0	-	-	-	-
	C: placebo	0	0	-	-	-	-

Footnotes

"-" denotes not reported

C: comparator; I: intervention

Appendix 11. Adverse events (III)

Characteristic	Intervention(s) and comparator(s)	Specific adverse events [description]	Specific adverse events [N]	Specific adverse events [%]
Ludvik 2002	I1: sweet potato (Caiapo) tablets 2 g	-	-	-
	I2: sweet potato (Caiapo) tablets 4 g	-	-	-
	C: placebo	-	-	-
Ludvik 2004	I: sweet potato (Caiapo) tablets 4 g	-	-	-
	C: placebo	-	-	-
Ludvik 2008	I: sweet potato (Caiapo) tablets 4 g	-	-	-
	C: placebo	-	-	-

Footnotes

"-" denotes not reported

C: comparator; I: intervention

Appendix 12. Survey of authors providing information on trials

Characteristic	Study author contacted	Study author replied	Study author asked for additional information	Study author provided data
Ludvik 2002	Y	N	N/A	N/A
Ludvik 2004	Y	N	N/A	N/A
Ludvik 2008	Y	N	N/A	N/A

Footnotes

N: no; N/A: not applicable; Y: yes

Appendix 13. Beta-cell function and insulin sensitivity

Parameter	Mean change (SE)	Between-group	P value	Comments

(Continued)

	Sweet potato (Caiapo) tablet	Placebo	difference (SE)		
Glucose AUC (g/dL) in 180 min	-4.17 (1.04)	0.68 (0.83)	-4.85 (1.33)	0.0001	Significant reduction in the Caiapo intervention group
Insulin AUC (mU/mL) in 180 min	-3.16 (1.04)	-0.99 (0.79)	-2.16 (1.31)	0.013	Significant reduction in the Caiapo intervention group
OGIS (ml/m^2/min)	28 (12)	6 (7)	22 (14)	0.034	Significant increase in insulin sensitivity in the Caiapo intervention group
Insulinogenic index (uU_{INS}/mg_{GLUC})	32 (23)	-15 (12)	47 (25)	0.081	No significant increase in insulin delivery to prevailing glucose level
Disposition index (common units)	127 (68)	-54 (39)	180 (79)	0.026	Significant increase in disposition index

Footnotes:

From Ludvik 2008

AUC: area under curve; GLUC: glucose; INS: insulin; min: minute(s); OGIS: oral glucose insulin sensitivity; SE: standard error

FEEDBACK

New feedback, 9 October 2013

Summary

The authors of this review treated the SD in the Ludvik 2004 article as SEM and converted them accordingly to do the meta-analysis and did the opposite to the Ludvik 2008 article in one analysis. Because the SD in the 2004 article was so small in comparison with the Ludvik 2002 and Ludvik 2008 articles, I agree with the authors that the SD in the 2004 article was most likely SEM, but I could not find conclusive evidence that these numbers were SEM rather than SD. In the 2002 (p.239, right lines 18-19) and 2008 (p.588, right line 11) articles, it was stated that all data were presented as mean ± SEM but the methods section and the legend of the relevant tables in the 2004 article explicitly stated that all data were presented as mean ± SD (p.437, statistics section and legends of both tables). Should the authors treat them as SD even though the authors said they were SEM? On the other hand, the numbers in the 2008 article were labeled as SEM but entered into the review as SD in some analyses (p.28, analysis 1.1) but not in others.

All three included articles compared the effect of Ipomoea batatas (Caiapo) by comparing the biochemical measures at the end of the trial. This review seemed to agree with this reasoning and synthesized the data accordingly. One could argue that this comparison was reasonable because randomization would balance the biochemical measures in each group, so there was no difference between the groups at the beginning of the trial. There are two reasons this was a suboptimal analysis of the data. First, equal biochemical measures between the groups was always achieved by randomization, especially in small groups. This was best illustrated in the 2002 article when Ludvik et al stated “this pilot study shows beneficial effects of high-dose caiapo on plasma glucose and total as well as LDL-cholesterol levels in patients with type 2 diabetes.” Inspection of the table 1 in the 2002 article showed the effect of high dose Caiapo treatment on total cholesterol was greatly inflated by the different baseline levels (6.05 vs. 4.97) in these two groups. The actual difference between low and high dose of Caiapo was close (0.37 vs. 0.52) and neither would have been statistically significant. Second, perhaps more importantly in general, treating related samples as independent samples wastes information and increases the variation of the measurements. This is a well described experimental design that should be analyzed with repeated measures tests in elementary statistics, yet many clinical trials do not seem to be aware of this method. Measuring the change in each individual before and after treatment greatly reduces the variance due to interpersonal variation. This effect will almost always increase the power of the trial. To see the magnitude of this effect, one can see table 3 of the article by Akilen[1] as an example (this second paragraph is trying to make a point similar to part of the comment I sent regarding CD007170 but with more detail).

References:

1. Akilen R., Tsiami A., Devendra D., and Robinson N. Treatment glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. Diabetic Medicine 2010;27:1159–67.

Reply

In all the three articles, the authors specifically mentioned that the results were presented as SEM in the respective methodology sections. These results were converted to SD accordingly using the equation: SD= SEM x √n. In Ludvik 2004 and Ludvik 2008, the results were presented in mg/dL. To standardise the results across the three studies, we converted all the results to SI units (mmol/L).

On the second paragraph: power calculation was lacking in Ludvik 2002 and could not justify the small number of only six participants per group. In addition to other issues of methodological quality, there were flaws in the statistics used. Although repeated measures were used in this study, this small number does not satisfy the criteria of using parametric statistical tests. We did not include the changes in lipid levels of this study in our analysis as changes over six weeks are not clinically meaningful. Similarly, in Akilen 2010, power calculation was lacking, in addition to other issues of methodological quality and external validity of the study.

Our additional comments: Type 2 diabetes mellitus is pandemic in many countries, particularly, in Asia. The advancement in the research of type 2 diabetes mellitus has enhanced the understanding of the complex progressive multi-pathophysiological nature of this disease that accelerates the aging process. For successful management, we need to consider issues beyond controlling glycaemia such as modifying cardiovascular risk factors as well as other risk factors for disability. Besides pharmacological management, non pharmacological means such as lifestyle modifications such like medical nutritional therapy, exercise and stop of smoking are also important. The increasing prevalence of patients in the younger age spectrum presents additional challenges. In view of the life-long affliction of the disease, the need for long-term complex treatments and the vulnerability of this population to irreversible disability that will escalate the burden of already pressured healthcare systems, the efficacies, benefits and safety of any new intervention for this disease need to be carefully scrutinised based on quality evidence.

Contributors

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For the authors: Cheow Peng.

WHAT'S NEW

Date	Event	Description
12 December 2013	Feedback has been incorporated	New feedback incorporated

HISTORY

Protocol first published: Issue 5, 2011
Review first published: Issue 2, 2012

Date	Event	Description
20 February 2013	New search has been performed	New search: no additional studies could be included
20 February 2013	New citation required but conclusions have not changed	No additional studies could be included

CONTRIBUTIONS OF AUTHORS

Cheow Peng Ooi (CPO): drafting, editing and submitting the review, designing search strategies and search for trials, selection of trials for inclusion/exclusion, extraction of data, entry of data; data analyses and data interpretations.

Seng Cheong Loke (SCL): independent input on trials selection,data analysis and data interpretations; input in drafting and general advice on the review.

DECLARATIONS OF INTEREST

Cheow Peng Ooi: none known.

Seng Cheong Loke: none known.

SOURCES OF SUPPORT

Internal sources

- Institute of Gerontology, Universiti Putra Malaysia, Malaysia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Cohen's kappa test for study selection, subgroup analysis and sensitivity analysis was not performed. We reported on outcomes of beta-cell function and insulin sensitivity.

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetes Mellitus, Type 2 [blood] [*drug therapy]; Glycated Hemoglobin A [metabolism]; Ipomoea batatas [*chemistry]; Phytotherapy [*methods]; Plant Extracts [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male