The safety and effectiveness of bitter melon (momordica charantia) as an alternative to traditional hypoglycemic agents for the control of fasting blood sugar in patients with type 2 diabetes mellitus: a systematic review protocol

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Review question/objective

This review will be guided by the following main research question:

Is the use of bitter melon an effective and safe alternative to traditional hypoglycemic agents for reducing fasting blood sugar in patients with type 2 diabetes mellitus?

Additional questions that will be addressed, with data permitting, are:

1. Does the efficacy and safety of bitter melon vary by frequency of consumption and dosage (amount consumed)?
2. Does the efficacy and safety of bitter melon differ by form of administration/consumption (for example, eating bitter melon versus drinking as a tea/diluting in water)?
3. Does the efficacy and safety of bitter melon differ in some sub-groups within this population of patients with type 2 diabetes, such as sex and age groups or groups with other chronic diseases and co-morbidities?

Background

Diabetes mellitus is a major global health problem with increasing prevalence. For all age groups worldwide, the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.\(^1\) Diabetes mellitus is characterized by chronic hyperglycemia and postprandial hyperglycemia, both leading to enhanced micro- and macro-vascular morbidity and overall mortality.\(^2,3\) Diabetes mellitus is further categorized into type 1 (T1DM) and type 2 (T2DM). T1DM is due to defect or damage of the islet cells of the pancreas leading to an absolute deficiency of insulin; T2DM is usually due to failure of the bodily tissues to respond to insulin. T2DM is associated with older age, obesity, positive family history, impaired glucose metabolism, physical inactivity and ethnicity.\(^4-6\)

Complementary and alternative medicine (CAM) is an approach that embraces a wide range of therapeutic practices and diagnostic systems that stands separate from Western or conventional medicine for specific conditions or overall well-being.\(^7,8\) Complementary refers to using a non-mainstream approach together with conventional medicine; alternative refers to using a non-mainstream approach in place of conventional medicine.\(^8\) The National Center for Complementary and Alternative Medicine (NCCAM) classifies CAM therapies into five categories, one of which is biologically-based therapies that use herbs and other dietary supplements as alternatives to mainstream Western medical treatment.\(^8\) A study has estimated that up to 30% of patients with diabetes mellitus use CAM.\(^9\)

Bitter melon, commonly known as momordica charantia, karela, balsam pear or bitter gourd, is the most frequently used plant for the treatment of diabetes mellitus amongst patients with this condition in Asia, South America, the Caribbean and East Africa.\(^10\) The ancient Ayurveda text for medicinal plants, the Nighantus, mentioned the therapeutic use of karela in the 15\(^{th}\) Century.\(^11\) In China, the earliest mention of using bitter melon for diabetes-related symptoms was also in the 15\(^{th}\) Century, found in the Yunnam Materia Medica written by Lan Mao.\(^12\)
The anti-diabetic and hypoglycemic effects of bitter melon have been widely studied in laboratories. Biochemical and animal model experiments have produced abundant data and hypotheses to account for such effects. These research studies suggest that bitter melon improves glucose tolerance, suppresses postprandial hyperglycemia in rats, and that bitter melon extract can enhance insulin sensitivity and lipolysis. Some studies have shown that the hypoglycemic effect of bitter melon was comparable with oral medications such as tolbutamide, chlorpropamide, and glibenclamide. Extensive biochemical data have shed light upon the possible mechanisms of the anti-diabetic actions of bitter melon, with the recurring theme being activation of the AMP-activated protein kinase system. Other studies suggested a role of the α- and γ-peroxisome proliferator-activated receptors (PPARα and PPARγ), which are pivotal in lipid and glucose hemostasis and may mitigate insulin resistance. Recently, a Zn-free protein bearing insulinomimetic activity was isolated from bitter melon, that echoed the idea of “vegetable insulin” that was termed 30 years ago.

At the time of writing this systematic review protocol, no large scale studies were found reporting negative side-effects of bitter melon. Years of its consumption as a dietary supplement and ethno-medicine in various countries do suggest a high level of safety. However, there have been isolated reports of hypoglycemic comas in children after drinking bitter melon tea, and one report of death due to consumption of bitter melon fruit. The bitter melon seeds contain a lectin that can inhibit protein synthesis in the intestinal walls of an animal model, but they produce no gastrointestinal symptoms in humans, except for a report of headache. Bitter melon seeds may also induce favism in humans—a condition caused by deficiency of glucose-6 phosphate dehydrogenase in the erythrocytes, while in animals, bitter melon fruit can lead to depressed fertility and induced abortion. In one clinical study, gastrointestinal symptoms such as abdominal discomfort and diarrhea have been reported.

In a cursory review of the literature on the hypoglycemic effects of bitter melon, it was found that there are clinical studies with human participants published in the English language, but they are relatively sparse. Within the existing studies, methodology differs widely, most notably with respect to the forms of bitter melon administration (from methanol extract, dried powder to fresh fruit), the actual dosage (timing and dose per kilogram of body weight) and the outcome measures (from HBA1c, post-prandial sugar levels to oral glucose tolerance test). Some studies have reported a better efficacy for bitter melon when taken in fresh or juiced form; some other studies have provided data that seem to support an acute or a single dose effect of bitter melon rather than a long term effect more than four weeks. There have been various forms of use of bitter melon (cooked, frozen, dried, and fresh) and different methods of administration (subcutaneous injection, ingestion) suggested in the literature and these have led to diverse, even conflicting results. Hence, a systematic review to address the proposed questions is valuable in that it would, by critically appraising and summarizing the existing evidence base, enhance understanding about the clinical efficacy and safety profile of using bitter melon in treating diabetes.

Checks in the JBI, PROSPERO, MEDLINE and CINAHL databases have been performed and no systematic reviews on the proposed topic appear to have been done before. A few systematic reviews have been conducted on the use of complementary and alternative medicine for the treatment of type 2 diabetes and are available on MedLine; however, they do not appear to be true systematic reviews in
terms of methodological rigor and/or they investigate multiple alternative treatments, with bitter melon being just one of them. Also, a search of the Cochrane Library revealed one systematic review on bitter melon for type 2 diabetes that was published in August 2012. This review searched 80 relevant studies published up to November 2010 in major English and European-based databases and selected four RCT designs for review. However, a large number of studies about the efficacy of bitter melon in the treatment of T2DM have been conducted in Asian countries such as China and Korea, published in non-English language journals and collected in non-English or non-European-based databases; but those studies and their results are rarely included in any English and European-based systematic reviews. A unique feature of the proposed systematic review is that coverage of studies for consideration will be extended to include Chinese and Korean literature about the safety, risk and effectiveness of bitter melon as an alternative to traditional hypoglycemic agents for the control of fasting blood sugar in patients with type 2 diabetes. One of the authors on this review is bilingual in the Chinese and English languages and had professional training in Chinese-English translation. A Korean clinical researcher who is proficient in the English language will also join the team conducting this systematic review.

The value of this review needs to be understood in the context of expert opinion and research suggesting that over time, patients often develop noncompliance with the treatments for type 2 diabetes commonly used, such as lifestyle management, oral medications and insulin. As a vegetable plant that easily grows from the soil, bitter melon is a potential candidate for a novel drug discovery, if its anti-diabetic potential is proven and its safety for use has been established, at least in the majority of the population with type 2 diabetes.

**Keywords**

blood glucose control; phytotherapy; hypoglycemic agent

**Inclusion criteria**

**Types of participants**

This review will consider studies that include children, adults and elders who have type 2 diabetes and are controlling their fasting blood sugars with oral hypoglycemic agents and insulin. If the patients with type 2 diabetes in the selected studies indicate variant individual characteristics such as age (i.e., young children or very old people), co-morbidities and other chronic diseases, they will be sub-grouped according to these characteristics. Sub-group analyses will shed light on nuances in efficacy and harm/safety of bitter melon in individuals with different characteristics.

**Types of intervention(s) and comparator(s)**

This review will consider quantitative studies that have evaluated the effectiveness of any dose of bitter melon as an alternative to traditional hypoglycemic agents for the treatment of type 2 diabetes mellitus. Studies that have examined the effectiveness of interventions using all variations of frequencies and dosages of bitter melon will be considered. The review will also adopt an inclusive approach with respect
to mode of administration with all different types of administration, such as bitter melon taken in fresh fruit, juice, tea, capsules and tablets to be considered for inclusion.

This review will consider as comparators: (1) the use of placebos, (2) the use of pharmacotherapy alone or in conjunction with the standard diet (excluding the use of bitter melon) that is recommended to patients with type 2 diabetes.

**Types of outcomes**

This review will consider studies that have measured impact on the following outcomes using a range of measures: (1) fasting blood sugars, Hba1c, (2) safety/harmful effects of bitter melon on patients with type 2 diabetes. Whilst these are the outcomes for which results will be sought, additional outcomes for which results are presented in studies that meet the inclusion criteria and pass critical appraisal will be considered.

**Types of studies**

This review will consider any experimental study designs including randomized controlled trials (RCTs), non-randomized controlled trials, quasi-experimental and before and after studies.

**Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract and of the index terms used to describe the articles. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference lists of all identified reports and articles will be searched for additional studies. Studies published in English, Korean and Chinese (traditional and simplified) will be considered for inclusion in this review. There will be no date exclusion for this review, other than the limits of the databases searched.

The databases to be searched for published studies will include:


The search for unpublished studies will include:

Google Scholar, SIGLE, Olster, Mednar, Proquest Dissertations and theses database, Networked Digital Library of dissertations and theses.

Initial keywords to be used will be:

Exp Diabetes mellitus, Type 2/

((typ$ 2 or typ$ II) adj diabet$).mp.

(diabet$ and (non insulin$ depend$ or noninsulin$ depend$ or non insulin depend$)).mp.
NIDDM.mp.
Exp Hypoglycemic agents/
((antidiabet$ or anti diabet$) adj (drug$ or agent$ or compound$)).mp.
(hypoglyc?emic adj (drug$ or agent$ or compound$)).mp.
Momordica charantia/
Phytotherapy/
Exp Plants, Medicinal/
Exp Extracts, plant/
bitter adj2 melon.mp.
momordica charantia.mp.
bitter adj2 gourd.mp.
karela.mp.
balsam adj2 pear.mp.
kugua.mp.
parya.mp.
pare ayam.mp.
pavayka.mp.
kayppayka.mp.
goya.mp.
nigauri.mp.
paakharkaai.mp.
hagalakayi.mp.
a"rea"h.mp.
kaakarakaya.tw.
ampalaya.mp.
muopdang.mp.
caraille.mp.
carilley.mp.
carilla.mp.
cerasee.mp.
cerase.mp.
karela.mp.
sopropo.mp.
kudret nari.mp.
faaga.mp.
karavila.mp.
blood glucose/
improve$ glucose control.mp.
(blood adj glucos$).mp. or (blood adj sugar$).mp.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (See Appendix I for the checklist that will be used to assess methodological quality). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data collection

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as weighted mean differences and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-square test. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Sub-group data analyses will be performed to examine whether or not the efficacy and safety/harmfulness of bitter melon varies according to other chronic conditions and co-morbidities, by frequency and dosage, by administration mode and across age and sex in patients with type 2 diabetes. Other important sub-group analyses will be conducted if additional themes emerge from the results of the included studies.
Conflicts of interest

None to disclose

Acknowledgements

The authors would like to acknowledge funding from the Canadian Institutes of Health Research for the Queen’s Joanna Briggs Collaboration.
References


Appendix I: Critical appraisal instruments

MAStARI appraisal instruments

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer ___________________________ Date ___________________________

Author ___________________________ Year ________ Record Number ______

1. Was the assignment to treatment groups truly random?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
2. Were participants blinded to treatment allocation?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
3. Was allocation to treatment groups concealed from the allocator?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
4. Were the outcomes of people who withdrew described and included in the analysis?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
5. Were those assessing outcomes blind to the treatment allocation?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
6. Were the control and treatment groups comparable at entry?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
7. Were groups treated identically other than for the named interventions?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
8. Were outcomes measured in the same way for all groups?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
9. Were outcomes measured in a reliable way?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐
10. Was appropriate statistical analysis used?  Yes ☐  No ☐ Unclear ☐ Not Applicable ☐

Overall appraisal:  Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

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**JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control**

Reviewer ___________________________ Date ___________________________

Author ___________________________ Year ______ Record Number ______

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<th>Yes</th>
<th>No</th>
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<tr>
<td>1. Is sample representative of patients in the population as a whole?</td>
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<td>2. Are the patients at a similar point in the course of their condition/illness?</td>
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<td>3. Has bias been minimised in relation to selection of cases and of controls?</td>
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<td>4. Are confounding factors identified and strategies to deal with them stated?</td>
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<td>5. Are outcomes assessed using objective criteria?</td>
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<td>7. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<td>8. Were outcomes measured in a reliable way?</td>
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Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (including reason for exclusion)
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## JBI Critical Appraisal Checklist for Descriptive / Case Series

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<td>1. Was study based on a random or pseudo-random sample?</td>
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<td>2. Were the criteria for inclusion in the sample clearly defined?</td>
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<td>5. If comparisons are being made, was there sufficient descriptions of the groups?</td>
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**Overall appraisal:** Include ☐ Exclude ☐ Seek further info ☐

Comments (including reason for exclusion)

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Appendix II: Data extraction instruments

MAStARI data extraction instrument

**JBI Data Extraction Form for Experimental / Observational Studies**

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**Study Method**

- [ ] RCT
- [ ] Quasi-RCT
- [ ] Longitudinal
- [ ] Retrospective
- [ ] Observational
- [ ] Other

**Participants**

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**Sample size**

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**Interventions**

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**Authors Conclusions:**

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Study results

Dichotomous data

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Continuous data

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