REVIEW ARTICLE

In Vivo Studies of *Lepidium meyenii* or Maca in Animal Models of Diabetes Mellitus and Other Metabolic Syndrome-Related Diseases- A Scoping Review

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ABSTRACT

Lepidium meyenii or Maca is a Peruvian plant that belongs to the Brassicaceae family. Maca has various attributed health benefits due to the diversity of its bioactive compounds. Studies reveal that Maca is effective for many purposes including in the treatment of diabetes mellitus (DM) and other metabolic syndrome-related diseases. This review aims to uncover previously identified underlying anti-diabetic effects of Maca as well as its potential in the treatment of other conditions linked to metabolic syndrome in animal models in vivo. A scoping review of the literature was conducted using a protocol by Arksey and O'Malley. The protocol centred on the identification of research questions, identification and selection of relevant studies, data charting and collating, summarizing, and reporting the findings. Searches were conducted using Semantic Scholar, Scopus, PubMed Central, and ScienceDirect. Six studies were included in the review. The studies varied in terms of purpose, methodology, and detail of findings. They include the administration of Maca in different types of animal models and its effect on several biochemical parameters. There is fundamental scientific evidence from this review that supports the anti-diabetic properties of Maca in animal models of DM and other metabolic syndrome-related diseases. However, the scarcity of reports indicates the need for more rigorous studies in the future.

Keywords
Lepidium meyenii; diabetes; metabolic syndrome (MetS); animal

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INTRODUCTION

Diabetes mellitus (DM) is a systemic metabolic disease characterised by changes in lipid metabolism, insulin resistance, and pancreatic β-cell dysfunction.[1] The global prevalence of DM is expected to continuously increase in the coming years, reaching 578 million (10.2%) and 700 million (10.9%) by 2030 and 2045, respectively.[2] According to the International Diabetes Federation (IDF), approximately 463 million adults worldwide were diagnosed with type 2 diabetes mellitus (T2DM) as of 2019. Furthermore, Southeast Asia has the highest prevalence of this disorder (8.8%), and Malaysia leads the Western Pacific region with a diabetes prevalence of 3.65 million (16.8%) out of 21.71 million adults in the country.[3]

DM is strongly linked to metabolic syndrome, a cluster of disorders that increase the risk of cardiovascular diseases.[4,5] The cluster includes abdominal obesity, insulin resistance, hyperlipidaemia, and hypertension.[5,6] Research on therapeutic approaches to DM and other metabolic disorders-related conditions is ongoing but comparatively inadequate given the disease burden. The search for medication with minimum to no side effects has led to the discovery of functional food and nutraceuticals as alternative treatments for these disorders. Traditional herbs are gaining popularity for their health benefits and supplementation for DM and other disorders associated with metabolic syndrome.[7] These studies regarding herbal medicines generally follow research guidelines for evaluating the safety and efficacy of herbal medicines published by the World Health Organisation in 1993 to help promote the use of scientifically validated herbal medicines to provide medical care cost-effectively.[8]

Maca grows at an elevation of over 4,000 metres in the Central Andes. In South America, the hypocotyl has been utilised for generations to improve fertility and vigour in

humans and animals.[9] Recent research has shown various medicinal benefits of Maca. It improves hormone secretion, immune system, and metabolism regulation, and has neuroprotective and anti-fatigue properties.[10-12] Maca is also used as a remedy for menopausal symptoms, premenstrual disorders, respiratory problems, rheumatism, and hyperglycaemia.[10] Despite Maca's reputation as a panacea, many previous studies have concentrated on its effect on fertility and sex drive instead of endocrine-related conditions.[10]

In the last decade, Maca has earned worldwide recognition for its health advantages.[9] As of mid-2021, the NIH Dietary Supplements Label Database (DSLD) reported 3,780 items with "maca" on the label, confirming its popularity. SciFinder shows a 550% increase in Maca-related papers from 2010 to 2020.[9] More recent studies now focus on Maca's health benefits beyond its fertility-boosting qualities. Despite the increased demand for treatment, there are few studies on Maca's effects on DM and other illnesses linked to metabolic syndrome. Several *in vivo* animal studies demonstrate that Maca improves cholesterol and glucose metabolism, protects liver cells from oxidative damage, and has antioxidant properties.[10,13,14] However, these statistics are not enough to verify Maca's effectiveness. Currently, there is no scoping review of this topic. The objective of this review is to identify and summarise available research evidence of Maca in animal models of DM and other disorders linked to metabolic syndrome.

METHODOLOGY

Scoping review protocol

A systematic literature review on the *in vivo* studies of *Lepidium meyenii* or Maca in animal models of DM and metabolic syndrome-related diseases was conducted. An Arksey and O'Malley-developed protocol served as the basis for this scoping review.[15] The five processes that make up the scoping review's structure are (i) identification of research questions, (ii) identification of relevant articles, (iii) selection of relevant articles, (iv) data charting, and (v) collating, summarising, and reporting the findings.

Identification of research questions

The basic principle of the scoping review is to identify the research question(s) that need to be addressed to build an effective search strategy. This scoping review aimed to find the answer to one research question: "What are the effects of *Lepidium meyenii* or Maca in animal models of DM and other metabolic syndrome-related conditions?".

Identification of relevant articles

Original peer-reviewed articles published in the English language between 2011 and 2021 were retrieved from extensive literature searches using four electronic databases namely Semantic Scholar, Scopus, PubMed Central, and ScienceDirect. The eligibility of six Boolean search terms used in this review was identified using Medical Subject Headings (MeSH). The final search terms were as follows: ("*lepidium meyenii*" OR maca) AND ("diabetes mellitus" OR "metabolic syndrome" OR high-fat diet OR rats).

Selection of relevant articles

All duplicates were deleted from the exported articles from the four databases. Inclusion and exclusion criteria were used to analyse the remaining publications. Both review criteria pertain to literature source, research type, and intervention kind. These criteria were used to pick reputable, relevant publications based on their titles and abstracts. Full articles of the papers that best answered the research topic were obtained. Two independent researchers then reviewed the entire article to determine if the shortlisted publications met the review's requirements. Both researchers accepted or rejected the article. When disagreements arose, the third and fourth researchers re-examined the publications to achieve a consensus. Table 1 lists inclusion/exclusion criteria.

Data charting

Once the articles were selected, several important data were extracted and transferred onto a data charting form using the database programme Excel. The data acquired were as follows:

i. Author(s), title of the article, publication year
ii. Study purposes
iii. Study population and sample size
iv. Characteristics of animal models
v. Types of disorder
vi. Methodology
vii. Intervention types
viii. Outcomes measures

Collating, summarizing, and reporting the findings

A content analysis was used to determine each study's primary criteria and to summarise its scope. We studied the selected articles to gain a general understanding of Maca and its effects in rodent models of DM and other conditions related to metabolic syndromes. The extracted data were subcategorized. The independent researchers then accepted or reformulated each subcategory. **Figure 1** depicts the study's scoping review process.

RESULTS

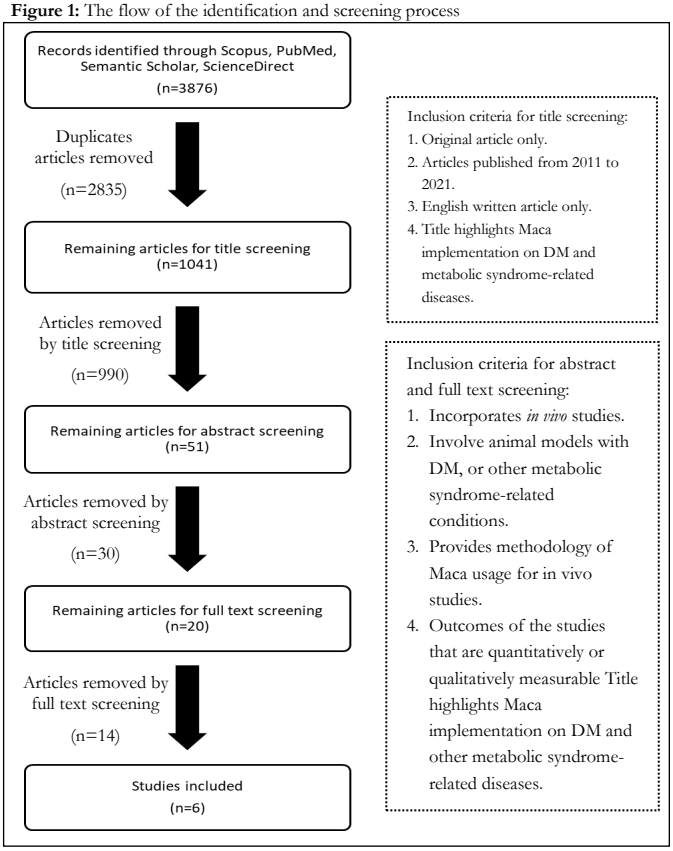
Literature search

Four databases were searched, and 1041 articles were found. Multiple duplicate articles were eliminated. From 1041 articles, 51 were accepted based on inclusion and exclusion criteria. Title-obscure publications were also appraised based on inclusion and exclusion criteria. 20 abstracts met Table 1's criteria for selection. After screening the complete versions of the 20 selected papers using both criteria, six were chosen for final review.

Table 1: Inclusion and exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Types and characteristics of sample	• Involves animal models • Animal models with DM or other metabolic syndrome-related conditions	• Involves human models
Methodology	• Provides detailed methodology of Maca usage for *in vivo* studies • Outcomes of the studies that are quantitatively or qualitatively measurable	• *In vitro* studies relating to Maca and DM or other metabolic syndrome-related diseases • Studies involving other plant species
Source of literature	• Original research articles written in English • Articles published from 2011 to 2021	• Book reviews, books, review articles, unpublished and published theses, and articles not written in English

Figure 1: The flow of the identification and screening process



Study characteristics

Animal models

All selected studies used rodents as the experimental animals as depicted in **Table 2**. Four out of six studies used rats,[8,10,16,17] one study used mice,[14] and one study used hamsters.[13] Data collected from the selected studies identified two studies that assessed the effect of supplementation of Maca on a rodent model of diabetes,[8,10] two studies on obesity,[16,17] and another two studies on other conditions linked to metabolic syndrome.[13,14]

To understand the pathophysiology of DM and other metabolic syndrome-related diseases in humans and to evaluate potential pharmacological treatments for the diseases, appropriate animal models are necessary. For this reason, various animal models have been developed. When conducting a study, the model must be carefully chosen; otherwise, the likelihood that a medicine or substance may fail in clinical trials due to problems with lower safety and effectiveness when applied to humans increases.[19] Rodents are the most used animals in animal experiments, accounting for approximately 80% of all

experimental animals.[20] However, while many rodent models exhibit certain metabolic syndrome symptoms, only a few can accurately replicate the whole spectrum of symptoms that represent these disorders in humans.

Rats are widely used in a variety of medical disciplines, primarily toxicology, obesity, social stress experiments, osteoporosis, diabetes, and neurobiology.[20] Wistar and Sprague-Dawley rats are the most often utilised among 51 species and 1000 strains.[20] Another study highlighted that mice are also one of the most often employed animal species when it comes to general pre-clinical testing. Previous studies have shown that polygenic mouse models of obesity, glucose intolerance, and diabetes can be used to explore genotypes and susceptibilities.[21] Despite passing preclinical trials, the Food and Drug Administration (FDA) estimated that 92% of drugs failed to reach the market in 2004. This failure rate is primarily attributable to genetic and physiological differences between species, but it is also possible for genetic and physiological differences within the same species to affect test results.[19]

Induction of DM and Metabolic Syndrome

Rodents can be genetically altered, given medications, or given nutritional changes to develop DM and other conditions linked to metabolic syndrome.[22] Streptozocin is the most common approach for inducing experimental diabetes in rodents, a condition that is frequently linked to metabolic syndrome. Streptozocin can either be used in combination with an altered diet or another chemical, such as nicotinamide, to induce T2DM, or it can be used alone in high dosages to establish type 1 diabetes (T1DM).[23,24] In two publications, a single intraperitoneal injection of a high dose of streptozocin produces significant damage to β-cells, which results in a lack of insulin secretion, a characteristic that is similar to T1DM.[8,10] Metabolic disorders and DM can also be brought on by manipulating the diet. Diet is essential for growth and development as a source of nourishment, however, the amount of nutrients a meal contains depends on how nutrient-dense it is. Increased caloric consumption has been associated with metabolic syndrome, cardiovascular diseases, and non-alcoholic fatty liver disease.[22] These human symptoms of metabolic syndrome have been mimicked in animals using combinations of high-fat and high-carbohydrate diets. According to two studies, feeding rodents a high-fat diet regularly will significantly contribute to excessive weight gain, a major risk factor for T2DM and cardiovascular diseases.[14,16,17,25] As demonstrated in two of the selected studies,[13,14] a combination of diets, such as high-fat/high-sugar and high-fat/high-fructose diets, can also be utilised.

Table 2: Summary of rodent models of DM and metabolic syndrome

Sources	Animal model and characteristics	Sample size	DM/ Metabolic syndrome induction	Treatment duration	Parameters measured
8	Species: Rat Strain: Wistar Age: - Sex: Male Weight: 180 g–200 g	30 (k=5; n=6)	STZ (50 mg/kg) via i.p. injection	21 days	• Wound contraction • Wound index • Bacterial counts • Dry and wet granulation weight • Hydroxyproline and hexosamine contents
16	Species: Rat Strain: Sprague–Dawley Age: 30 weeks old Sex: Male Weight: 300 ± 20 g	28 (k=4; n=7)	High-fat diet	60 days	• Insulin level • Insulin receptor substrate 1 (IRS1) level • Sirtuin 1 (SIRT1) level • Leptin level
14	Species: Mice Strain: - Age: - Sex: Male Weight: 18-20 g	80 (k=8; n=10)	High-fat/ High-sucrose diet	49 days	• Glucose level • Lipid peroxidation activity • Lipid profile e.g, cholesterol (CHO), triglycerides (TG), low-density lipoproteins (LDL), and high-density lipoprotein (HDL) levels • Neurobehavior-al activity
10	Species: Rat Strain: Wistar Age: 90 days old Sex: Male Weight: -	110 (k=11; n=10)	STZ (50 mg/kg) via i.p. injection	60 days	• Glucose level • Thiobarbituric acid reactive substances (TBARS) contents • Carbonylated protein content
17	Species: Rat Strain: Sprague -Dawley Age: 8 weeks old Sex: Male Weight: 200 ± 20 g	28 (k=4; n=7)	High-fat diet	56 days	• Nutrient digestibility • Expressions of nutrient transporters
13	Species: Golden Hamster Age: 6 weeks old Sex: Male Weight: -	48 (k=6; n=8)	High-fat, high-fructose diet	140 days	• Glucose level • Insulin level • Lipid profile e.g, CHO, TG, LDL, and HDL levels

Table 3: Types of Maca used in the selected studies

Sources	Types of Maca	Extraction and preparation method	Dosage and administration route
8	Black Maca	The ointment was prepared from hydroalcoholic extract of black maca roots enriched with benzyl glucosinolates through the trituration method in ceramic mortar and pestle	Maca was given as 5% and 10% w/w ointment and 200 mg/kg BW via oral administration
16	Black and red Maca	Maca powder consisted of a synergistic maca compositions, which comprise 4:1 black-red Maca root	Maca powder extract was administered through an intragastric tube (40 mg/kg BW)
14	Maca capsules	Each capsule contains 500 mg of Maca roots	Maca capsules were incorporated into the diet at 1, 2, and 4 g/kg of feed ad libitum
10	Black, yellow, and purple Maca	Maca was prepared by partitioning maca extract from dried roots with petroleum ether extract (0.05 g/ml)	Maca was administered at 100mg/kg orally via an intragastric tube (2ml/rat)
17	Black and red Maca	Maca roots powder compositions consisted of a synergistic compound of black and red Maca in a ratio of about 4:1 to about 1:4.	Maca powder extract was administered through an intragastric tube (40 mg/kg BW)
13	Black Maca	Aqueous extract of Maca was prepared by sonication and boiling of black maca powder before it was filtered. The concentrate was dissolved in an aqueous solution before use.	Maca was administered at 300 mg/kg, 600 mg/kg, and 1200 mg/kg via daily instillation

Types of Maca and their Properties after *in Vivo* Administration

Types of Maca

There are 13 known variants of Maca, ranging from white to black depending on the cultivar. Yellow Maca, the most popular commercially, accounts for 47.8% of all known variants.[26] These variations were named based on their hypocotyl colours.[27] These differences are also known as Maca ecotypes.[28] Maca 'variants' based on hypocotyl colour are similar yet may have different properties.[29] Table 3 highlights the Maca types employed in all evaluated research.[27]

Out of six studies, two studies used a formulated Maca composition comprised of a synergistic compound of black and red Maca in a ratio of about 4:1 to about 1:4.[16,17] One study used Maca in the form of a capsule.[14] A study also studied different types of Maca which were yellow- and purple-coloured Maca.[10]

Research has shown that the nutritional value, concentration, and presence of secondary metabolites vary depending on the colour of the Maca roots,[29] which may affect the results observed. This is particularly true for glucosinolates, macamides, and macaenes, except beta-sitosterol and campesterol. The exact substances responsible or active for certain diseases and their mechanisms of action are not yet fully understood. The fact that these substances are thought to be bioactive components makes them interesting among other substances. Purple Maca hypocotyls were found to be rich in macamide concentration while yellow hypocotyls had poor concentrations.[30] One study revealed that purple Maca had higher concentrations of n-benzyl-5-oxo-6E, 8E-octadecadienamide while yellow Maca had higher concentrations of macaenes. Red and purple Maca also contained more glucosinolates than yellow Maca.[30]

The relationship between colour type and metabolites still needs to be verified in more studies, but the available findings are suggestive of a correlation. These findings can be applied to the development of targeted functional products based on a patient's unique nutritional and therapeutic needs.[30]

Maca Preparation and Administration

The preparation of Maca is essential for achieving the desired biological effects. All of the chosen studies made use of various kinds of preparatory techniques from Maca roots. A study incorporated hydroalcoholic extract of black Maca with benzyl glucosinolates given as 5% and 10% w/w ointment prepared through trituration method in a ceramic mortar and pestle as well as 200 mg/kg BW p.o.[8] Another study prepared an aqueous extract of black Maca and administered it to the rodents at 300 mg/kg, 600 mg/kg, and 1200 mg/kg via daily instillation.[13] Black,

yellow, and purple Maca in one study were prepared by partitioning Maca extract with petroleum ether extract before orally administered via an intragastric tube.[10] Two of the chosen studies also administered Maca powder extract through an intragastric tube (40 mg/kg BW).[16,17] Meanwhile, another one incorporated Maca in capsule form into the diet at 1, 2, and 4 g/kg of feed ad libitum.[14] None of the studies mentioned in detail which specific part of Maca roots were used for extraction.[8,10,13,14,16,17]

Recent research focused on devising drying processes under controlled conditions to modulate the biochemistry of glucosinolate hydrolysis and optimise the bioactive compound content of root flour. Notably, the macamide and macaene content is dependent on the dehydration method and initial glucosinolate content. [31]

Traditionally, Maca is ingested after being boiled or extracted in alcohol. In experimental investigations, Maca aqueous extract is only effective after Maca hypocotyls have been pulverised and boiled in water.[26] The procedure of boiling appears to increase active metabolites. In fact, an increase in temperature influences the availability of numerous secondary metabolites in plants, with some metabolites increasing and others decreasing. Glucosinolates are an essential constituent of Maca. These compounds are heat-sensitive. However, other metabolites are increased by heating.[32]

Biochemical parameters

Oral Maca extracts reduced glucose levels in diabetic rodent models.[10,14] This was true for black, yellow, and purple-coloured Maca.[10,14] All varieties of Maca extracts lowered plasma glucose levels in DM rats and reduced STZ-induced oxidative stress, suggesting maca might ameliorate hyperglycaemia-induced oxidative stress.[10] However, in one study, high-fat/high-fructose-fed animals treated with black Maca extract (BME) had no change in blood glucose level.[13]

Aqueous black Maca-supplemented (600 and 1,200 mg/kg) hamsters showed decreased insulin levels and better insulin sensitivity.[13] These data validated that aqueous black Maca decreases HFD-induced hyperlipidaemia and hyperinsulinemia while enhancing insulin sensitivity, as evaluated by HOMA-IR.[13] In another study, control and Maca groups had higher fat and hepatic insulin levels than HFD and HFD+Maca groups.[16] In adipose tissue, the Maca group had the highest IRS1 levels compared to HFD and HFD+Maca.[16] Maca had the highest liver insulin expression but did not differ from the control. Maca and HFD differed by 19% ($p<.01$); HFD+Maca by 27.3% (p.001). Insulin levels were not affected by HFD ($p>.05$). The result suggested that lower insulin levels in obese rats may be related to insulin build-up, which adds to insulin resistance.[16]

Several researchers employed TBARS to measure lipid peroxidation by measuring total Malonaldeyde (MDA) levels. MDA is a lipid peroxidation biomarker and is a breakdown product of unsaturated fatty acids.[10,14] According to Olofinnnade *et al.* (2020), a high-fat/high-sucrose diet with 0.1, 0.2, and 0.4% Maca reduced MDA levels in rodents, indicating low lipid peroxidation and cell injury.[13] In another study, yellow and purple Maca exhibited a greater drop in TBARS levels than black Maca.[10]

Only two studies reported on CHO, TG, LDL, and HDL.[13,14] Maca at 0.1, 0.2, and 0.4% reduced total CHO, TG, and LDL while increasing HDL in rodents given a high-fat/high-sugar diet.[14] Another study found a similar tendency when rodents were given 300, 600, and 1200 mg/kg of aqueous BME.[13] Research found that aqueous BME increased liver secretion and excretion, protected liver cells, and reduced HFD-induced hepatic CHO and TG buildup.[13]

Though many researchers have examined how plant-based substances can regulate lipid and glucose metabolism, very few have specifically addressed Maca. Despite the lack of a defined mechanism, Maca glucosinolate has been shown to exhibit hypoglycaemic properties.[33,34] Preliminary studies suggest that Maca glucosinolate can regulate insulin resistance levels and improve glucose metabolism.[34,35] Benzyl glucosinolate and (2R)2hydroxy2phenethylglucos may be the primary active ingredients that could increase insulin sensitivity and exhibit the aforementioned biological activity.[34] The

results of this study suggest that glucosinolate-rich Maca ethanol extract decreases insulin resistance via activating PI3K/AKT in insulin-resistant HepG2 cells, which may have beneficial effects on treating or correcting lipid and glucose metabolic disorders.[34]

LIMITATION

The lack of article quality assessment is a limitation of this scoping review. This, however, is a general feature of scoping reviews, as their objective is to identify research rather than evaluate its quality.[15] Relevant material may have been excluded because only English-language papers were included. This scoping review focuses on contemporary Maca treatments for DM and other metabolic syndrome-related conditions, hence literature before 2011 was excluded. However, due to the continual progression of the treatment for these diseases, older findings may no longer be applicable. Another limitation of this study is the lack of histological studies of the pancreas and liver, the body's most important metabolic organs, which regulate homeostasis and lipid and glucose metabolism.[36]

CONCLUSION

This review found a fair amount of fundamental scientific evidence supporting Maca's anti-diabetic properties in animal models of DM and other metabolic syndrome-related diseases. Most of the literature focuses on the effects of Maca extracts on rodents through the assessment of various biochemical parameters such as glucose, lipid profile, and serum insulin levels. Maca intervention significantly improved metabolism disorder by regulating the glycolysis/gluconeogenesis-TCA cycle pathway and modulating the expression levels of genes involved in the PPARα signaling pathway, according to data from selected literature. As a result, Maca has the potential to be a dietary supplement for preventing or slowing the progression of lipid and glucose metabolism disorders. However, all the studies accepted by this review only focused on Maca root extract in its crude compound form. Studies and clinical trials focusing on the effectiveness of isolated proposed active components of Maca such as Maca amide and benzyl glucosinolate are important areas for future research.

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