Employment of *Eugenia uniflora* in glycemic control and prevention of diabetes mellitus complications: a systematic review and meta-analysis

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease with considerable morbidity and mortality. The use of medicinal plants, such as *Eugenia uniflora* L., is a promising adjuvant in the treatment of this disease. This systematic review and meta-analysis aimed to evaluate the effects of *E. uniflora* on glycemic control and prevention of DM complications. Searches were performed in Pubmed/Medline, Web of Science, Scopus and Embase databases. Eligibility criteria were clinical or *in vivo* preclinical trials that evaluated the use of *E. uniflora* in glycemic control and prevention of DM complications, written in English, French, Spanish and Portuguese. Three preclinical *in vivo* trials were included in the systematic review and two in the meta-analysis. All studies demonstrated that the administration of *E. uniflora* provided a beneficial result in glycemic control. Positive results were also observed in DM comorbidities and complications. In the meta-analysis, it was evidenced that the animals that received *E. uniflora* had reduced levels of glucose and triglycerides in relation to those that did not receive the treatment. Thus, *E. uniflora* helps in glycemic control and DM complications. However, it is necessary to carry out clinical trials to evaluate its use in patients with DM.
Keywords: Blood glucose; Hyperglycemia; Phytotherapy; Plants; Medicinal.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease characterized by a deficiency in the secretion of the hormone insulin and/or in the absence of its action (Rodacki et al. 2021). Chronic non-communicable diseases (NCDs), including DM, are present worldwide and are responsible for the main causes of death (World Health Statistics 2021). In 2021, it was found that 537 million people aged between 20 and 79 years had DM in the world and that this number will reach 649 million in 2030 (International Diabetes Federation 2021).

In 2021, Brazil ranked sixth among the top ten countries with the highest number of patients, between 20 and 79 years old, with type 2 diabetes mellitus (T2DM) and the estimate is that in 2045 this number will be 23.2 million. In addition, Brazil ranks third in the ranking of countries with the highest rate of type 1 diabetes mellitus (T1DM) among children and adolescents aged 0 to 19 years old. Due to the high prevalence of DM in Brazil, the costs for treatment are high and, for this reason, the country is the third with the highest expenses on DM between 20 and 79 years old, with an expense of about 49, 2 billion dollars in therapeutic resources for this age group (International Diabetes Federation 2021).

Long-term hyperglycemia, resulting from the lack of adequate control of DM, generates vascular lesions that are responsible for chronic complications. These complications can be both macrovascular and microvascular and are mainly caused by advanced glycation end products (AGEs). Microvascular lesions include nephropathy, retinopathy and neuropathy. Those that affect the brain, heart and lower limbs are called macrovascular (Tschiedel 2014).

The treatment of DM is performed with the use of oral hypoglycemic agents and/or insulin (Rodacki 2021). However, the use of some medicinal plants in the treatment of DM is very promising,

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as it can contribute to the reduction of the dose of conventional drugs and the risk of occurrence of adverse reactions, in addition to providing better therapeutic success (Salehi et al. 2014).

In 2006, the Brazilian National Policy on Medicinal Plants and Phytotherapeutics was created and its objective is to guarantee the safety and correct use of plants, in addition to enabling the sustainable use of biological diversity (Brazil 2006). In February 2009, the Brazilian National List of Medicinal Plants of Interest to the Unified Health System (RENISUS) was published. RENISUS consists of a list of 71 popularly known and scientifically proven plant species (Brazil 2009).

Among the plants present in RENISUS is *Eugenia uniflora* L. that belongs to the Myrtaceae family. *E. uniflora* has an edible fruit and is present from the Amazon to Rio Grande do Sul, which justifies its easy access in Brazil (Auricchio and Bacchi 2003; Vizzotto 2006). It is used in folk medicine due to its many therapeutic benefits, highlighting its anti-goat, anti-rheumatic, digestive, hypoglycemic and hypotensive action (Braatz et al. 2018).

With the increasing numbers of people with DM in the world and the high risk of chronic complications, the need for alternative treatments that are effective, safe and low cost is evident. Due to the therapeutic activity of *E. uniflora* as a hypoglycemic agent and antioxidant, in addition to its safety and easy access by the population, its use has great potential to assist in the glycemic control of patients with DM and in the prevention of chronic complications (Queiroz et al. 2015; Peixoto et al. 2021).

However, high-quality scientific evidence is still needed to support the rational use of these plants by the population. Thus, the objective of this study was to carry out a systematic review and meta-analysis in order to understand the benefits that this species offer in glycemic control and in the complications and comorbidities related to DM.

METHODS

Search strategy

The search for scientific articles in the literature was carried out independently by two people in the Medline (PubMed), Web of science, Scopus and Embase databases. The selection was performed using the descriptors “diabetes mellitus, type 2” and “diabetes mellitus, type 1” and their respective *entry terms* in combination with the descriptor “Eugenia” and its *entry terms*, using the “AND” connector between the terms. The definition of descriptors was done through the Medical Subject Headings (MeSH).

The search was limited to articles published in English, Spanish, Portuguese or French. There was no limitation regarding the year of publication of the articles.

Eligibility Criteria

Eligibility criteria were established in accordance with checklist Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Page et al. 2021 and comprised clinical trials or *in vivo* preclinical trials, which analyzed the use of *E. uniflora* in glycemic control and/or prevention of DM complications. In the systematic review, only articles were included in which the experimental design made it possible to differentiate the points in relation to the acronym PICOS:

- Population: patients or animals with DM.
- Intervention: administration of extract, fractions, subfractions or isolated substances of *E. uniflora*.
- Control: patients or animals with DM that did not receive *E. uniflora*.
- Outcome: improvement in glycemic control and/or prevention of DM complications.
- Study design: *in vivo* preclinical trial or clinical trial.

Studies that evaluated the use of *E. uniflora* in combination with other substances, that is, those that did not evaluate the use of *E. uniflora* apart, were excluded. Secondary studies (systematic reviews, narrative reviews), *in vitro* experimental studies, conference or symposium documents, letters, editorials, case reports were also excluded. The search for articles in the databases was carried out until August 10, 2021.

Selection of articles

The choice of articles took place in two stages, which were carried out by two people independently. In the first step, duplicate articles were disregarded, followed by a previous reading of the titles and abstracts in order to add only the clinical trials or *in vivo* preclinical trials written in English, Portuguese, Spanish or French that analyzed the use of *E. uniflora* in glycemic control and/or prevention of DM complications. In the second stage, the pre-selected articles were submitted to full text reading in order to assess the eligibility criteria for possible inclusion in the study. Thus, following the guidelines of PRISMA (Page et al. 20021), a flowchart was created to simplify how many articles were included or excluded in each step related to the established criteria.

Data extraction from selected articles

From the studies included in the systematic review, the following data was obtained for the construction of tables: plant species, dose administered, route of administration, duration of treatment, method of obtaining the plant derivative, chemical

markers, type of mouse, size of the control and intervention group, type of DM, DM induction method, blood glucose measurement method, results obtained in glycemic control, complications and comorbidities of DM analyzed and results obtained for complications and comorbidities of DM. The extraction of these data was performed by two people independently.

Assessment of the quality of studies

The quality of *in vivo* preclinical studies was independently analyzed by two people using the SYRCLE tool which contains different biases for evaluation, namely: selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. Thus, for each selected article, ten questions were asked in order to classify the risk of bias. When the answers were "YES" the risk of bias was classified as low and "NO" answers indicate a high risk of bias. For questions with uncertain answers, the risk of bias was classified as "UNCERTAIN". This tool is qualitative, that is, it is not indicated for summing the scores of each study in isolation (Hooijmans et al. 2014).

Meta-analysis

Meta-analyses were performed with the articles included in the systematic review that presented the same design and evaluated the same type of DM and analyzed the same outcome. For the accomplishment of the meta-analyses, the mean, the standard deviation and the sample size of the intervention group and of the control group were used and, later, the difference of the mean between them was calculated. To assess the heterogeneity of the studies, the I^2 test was used, where those with an $I^2 > 50\%$ and a p-value < 0.10 are considered heterogeneous. In the calculations of the meta-analyses, fixed-effect model was used for studies classified as homogeneous and random-effect model in the presence of heterogeneity. The statistical program Review Manager (RevMan) version 5 was used to perform the meta-analyses.

RESULTS

Figure 1 is a flowchart that summarizes the steps of the selection of articles. A total of 2380 articles were found in the databases (18 in PubMed/Medline, 21 in Web of Science, 2782 in Scopus and 336 in Embase). A total of 777 articles from Scopus were excluded after application of the filter for language and type of document and 73 were excluded because they were duplicated, totaling 2307 articles for initial screening. In the initial screening, 2303 articles were excluded because they did not meet the eligibility criteria, leaving 4 articles for analysis of the full text, in which one article was excluded for not presenting control group. Thus, 3 articles were included in the systematic review. One article that evaluated type 1 diabetes mellitus (T1DM) was excluded and two articles that evaluated type 2 diabetes mellitus (T2DM) were included in the meta-analysis.

All the three articles included in the systematic review were *in vivo* preclinical trials (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019). Clinical trials were not found.

Table 1 describes the characteristics of the articles included in the present study, which were published between the years 2017 to 2019. Among the selected articles, one used the leaves and two the fruits of *E. uniflora* (Oliveira et al. 2017; Cardoso et al. 2018), and the oral route was used for administration in all articles included (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019).

Obtaining the vegetable derivative consisted of the method of spraying, maceration in methanol, evaporation, lyophilization, suspension in water, extraction in butanol and fractionation by column chromatography by one study (Sobeh et al. 2019) and two used the method of freezing, sonication in ethanol-water, removal of ethanol under reduced pressure and lyophilization (Oliveira et al. 2017; Cardoso et al. 2018).

In the three selected articles, procedures were carried out to identify chemical markers present in the species. All of them had flavonoids in their chemical composition (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019), one observed the existence of tannins and dilactone of valoneic acid (Sobeh et al. 2019) and two had anthocyanin (Oliveira et al. 2017; Cardoso et al. 2018).

Two articles evaluated T2DM (Oliveira et al. 2017; Cardoso et al. 2018) and one analyzed T1DM (Sobeh et al. 2019). All of them used male Wistar rats (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019) and only one also used Swiss albino mice (Sobeh et al. 2019). One study presented an intervention group and a control group with ten rats (Sobeh et al. 2019), one employed 8 rats (Cardoso et al. 2018) and one had a range of 5 to 10 rats in each group (Oliveira et al. 2017). The rats belonging to the intervention and control groups underwent different DM induction methods: in one article, DM was induced by streptozotocin (60 mg/kg) in a single intraperitoneal dose (Sobeh et al. 2019); one by dexamethasone also intraperitoneally (Cardoso et al. 2018) and one by sucrose-enriched diet (Oliveira et al. 2017). Blood glucose was assessed in all studies, and the procedure used for blood glucose measurement was not reported in one study (Sobeh et al. 2019) and in two studies it was measured using a glucometer and the colorimetric enzymatic

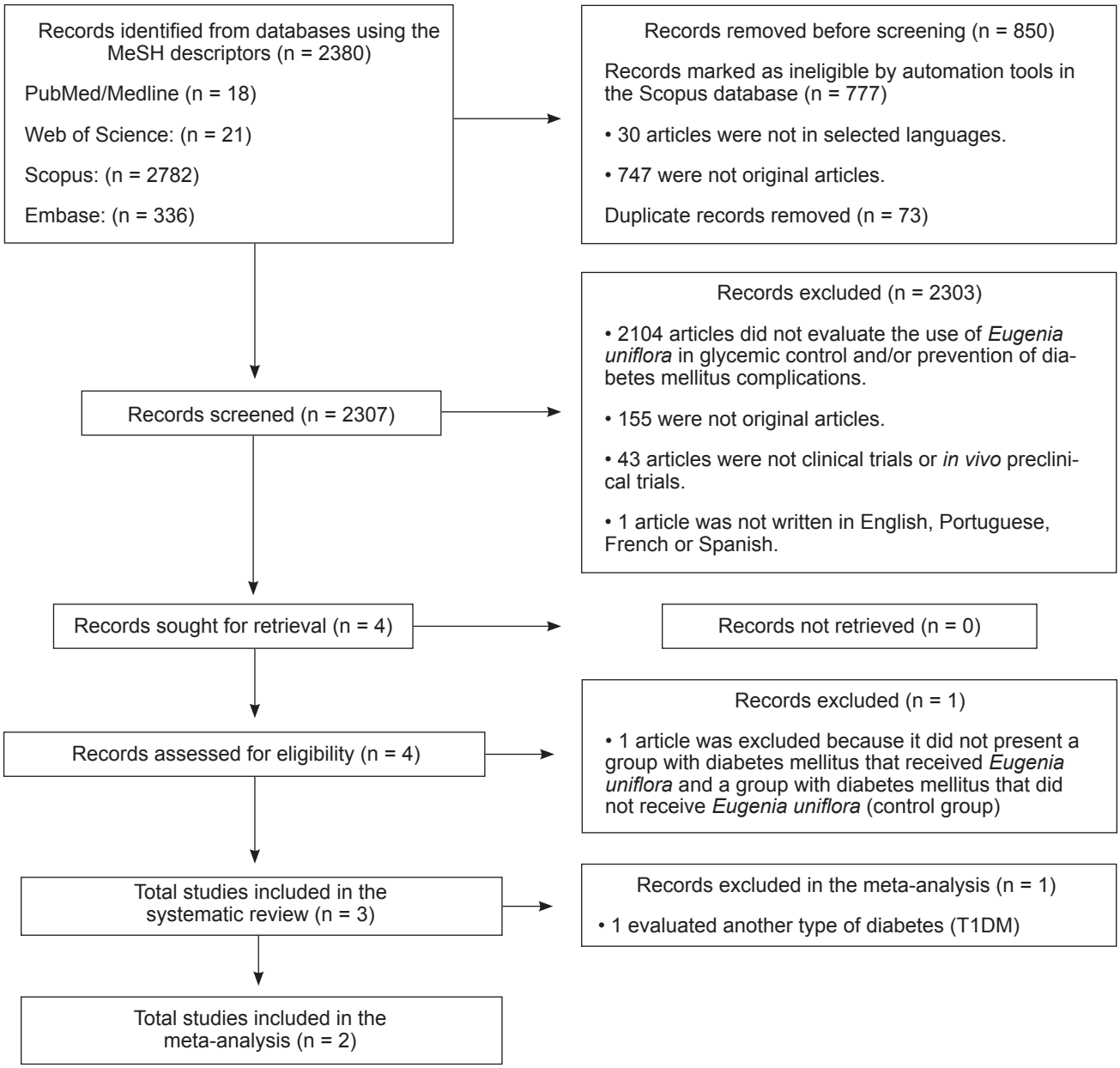

Figure 1. Flowchart of the selection of articles included in the systematic review and meta-analysis according to the eligibility criteria.

method (Oliveira et al. 2017; Cardoso et al. 2018).

Table 2 shows the results obtained for glycemic control and for complications and comorbidities of DM in the selected studies. All articles obtained a positive result in relation to glycemic control (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019). The three *in vivo* preclinical trials showed significantly lower serum glucose levels in the intervention group compared to the control group after treatment (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019); one of them had a significant increase in serum insulin concentration in the intervention group after treatment (Sobeh et al. 2019) and in other the prevention of glucose intolerance was observed after the use of *E. uniflora* (Oliveira et al. 2017).

Among the results observed in the complications and comorbidities of DM, two evaluated the results in dyslipidemia (Oliveira et al. 2017; Cardoso et al. 2018), and in one of them there was a significant reduction in the serum levels of triglycerides (Cardoso et al. 2018) and in the other there was a significant decrease in the serum levels of triglycerides, low density lipoprotein (LDL) cholesterol and total cholesterol (Oliveira et al. 2017). In one study only lipid peroxidation was evaluated and there was a significant reduction in lipid peroxidation levels after intervention with *E. uniflora* (Sobeh

Table 1. Characteristics of the studies that analyzed the use of *Eugenia uniflora* in glycemic control and/or prevention of DM complications and were included in the systematic review.

Author, year	Sobeh et al. (2019)	Cardoso et al. (2018)	Oliveira et al. (2017)
Part of the plant used	Leaves	Fruits	Fruits
Dosage administered / route of administration	100 mg/kg/day oral	200 mg/kg/day oral	200 mg/kg/day oral
Duration of treatment	10 days	21 days	150 days
Method of obtaining the vegetable derivative	Spraying, maceration in methanol, evaporation, lyophilization, suspension in water, extraction in butanol, fractionation by column chromatography	Freezing, sonication in ethanol-water, filtration, removal of ethanol under reduced pressure and lyophilization	Freezing, sonication in ethanol-water, filtration, removal of ethanol under reduced pressure and lyophilization
Chemical markers	Tannins, flavonoids and valoneic acid dilactone	Phenolic compounds, flavonoids and anthocyanins	Phenolic compounds, flavonoids and anthocyanins
Rat type	Adult male Wistar rats and Swiss albino mice	Wistar rats	21 days old male Wistar rats
IG and CG size	10 and 10	8 and 8	5-10 and 5-10
Type of DM	T1DM	T2DM	T2DM
DM induction method	Streptozotocin (60 mg/kg) in single dose intraperitoneal route	Dexamethasone intraperitoneal route	Sucrose-enriched diet
Blood glucose measurement method	NI	Glucometer and colorimetric enzymatic method	Glucometer and colorimetric enzymatic method

IG: intervention group; CG: control group; DM: diabetes mellitus; NI: not informed; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.

et al. 2019). Another study also analyzed the diabetes kidney disease, but did not show significant differences for urea levels (Oliveira et al. 2017).

Table 3 shows the results found for the quality of studies according to the SYRCLE tool (Hooijmans 2014). Regarding selection bias, all analyzed articles showed low risk of bias for allocation series and baseline characteristics and high risk of bias for allocation concealment (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019). In the evaluation of performance bias, all were classified as having low risk of bias for random placement and high risk of bias for blinding (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019). For detection bias, all studies were considered to be at high risk of bias for random outcome assessment and blinding (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019). Regarding attrition bias, one article had a low risk of bias (Sobeh et al. 2019) and two had a high risk of bias for incomplete outcome (Oliveira et al. 2017; Cardoso et al. 2018). Regarding reporting bias, all were assessed as low risk of bias for selective reporting of the outcome (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019). None of the articles presented other sources of bias, so all were categorized as low risk of bias (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019).

Figures 2, 3 and 4 refer to the meta-analyses performed and two preclinical studies were included in this step, which evaluated the same type of DM (T2DM) and the same outcome (glycemia, serum levels of triglycerides and total cholesterol) (Oliveira et al. 2017; Cardoso et al. 2018). The ran-

Table 2. Results obtained in studies that analyzed the use of *Eugenia uniflora* in glycemic control and/or prevention of DM complications and were included in the systematic review.

Author, year	Results obtained in glycemic control	DM complications and comorbidities analyzed	Results obtained in DM complications and comorbidities
Sobeh et al. (2019)	Serum glucose levels were significantly lower in the IG compared to the CG (p<0.0001) and serum insulin levels were significantly higher in the IG compared to the CG (p<0.0001)	Lipid peroxidation	Lipid peroxidation was significantly lower in the IG compared to the CG (p<0.0001)
Cardoso et al. (2018)	Serum glucose levels were significantly lower in the IG (102.36 ± 6.05 mg/dl) compared to the CG (156.55 ± 8.20 mg/dl) (p<0.001)	Dyslipidemia	Serum triglyceride levels were significantly lower in the IG (91.67 ± 4.81 mg/dl) compared to the CG (177.40 ± 3.57 mg/dl) (p < 0.001). There was no significant difference between the groups regarding total cholesterol
Oliveira et al. (2017)	Serum glucose levels were significantly lower in the IG (82.10 ± 2.84 mg/dl) compared to the CG (128.86 ± 6.79 mg/dl) (p<0.001). The sucrose-enriched diet induced glucose intolerance and treatment with *Eugenia uniflora* prevented it	Dyslipidemia and diabetes kidney disease	Serum total cholesterol levels were significantly lower in the IG (109.4 ± 1.63 mg/dl) compared to the CG (156.8 ± 5.72 mg/dl) (p < 0.001). Serum LDL cholesterol levels were significantly lower in the IG (45.87 ± 4.07 mg/dl) compared to the CG (100.3 ± 2.83 mg/dl) (p < 0.001). Serum triglyceride levels were significantly lower in the IG (56.60 ± 3.66 mg/dl) compared to the CG (98.00 ± 3.20 mg/dl) (p < 0.01). There was no significant difference between the groups with respect to HDL cholesterol and urea

DM: diabetes mellitus; IG: intervention group; CG: control group; LDL: low density lipoprotein; HDL: High density lipoprotein.

Table 3. Evaluation of the quality of studies according to the SYRCLE tool.

Author/Year	Selection Bias			Performance Bias		Detection Bias		Atrition Bias	Reporting Bias	Other Sources of Bias
	1	2	3	4	5	6	7	8	9	10
Sobeh et al. (2019)	Y	Y	N	Y	N	N	N	Y	Y	Y
Cardoso et al. (2018)	Y	Y	N	Y	N	N	N	N	Y	Y
Oliveira et al. (2017)	Y	Y	N	Y	N	N	N	N	Y	Y

Y (YES) – low risk of bias; N (NO) – high risk of bias. Source: Hooijmans et al. 2014
1- Allocation series: Random distribution of control and intervention groups (which received *Eugenia uniflora*) in all articles; 2- Baseline characteristic: Both the intervention group and the control group manifested type 1 or type 2 diabetes mellitus in all articles; 3- Allocation concealment: It was not reported in any article whether there was concealment in the designation of the control and intervention groups; 4- Random housing: The distribution of the control and intervention groups happened randomly between housing and they were submitted to the same conditions; 5- Blinding: It was not described in any article whether the researcher was aware of which animals received *Eugenia uniflora* or placebo; 6- Random evaluation of the outcome: No article reported whether the analysis of the outcome of the control and intervention groups was done randomly; 7- Blinding: It was not reported in any article whether the researchers knew which animals had received *Eugenia uniflora* or placebo in the evaluation of the outcome; 8- Incomplete outcome result: In two articles the outcome had the same number of animals present at the beginning of the study and in two articles it was not specified whether the same number of animals was used at the beginning of the study and at the outcome; 9- Selective outcome reporting: There was no selective outcome reporting for results that were significant in any article because all outcomes were described; 10- Other sources of bias: No other sources of bias were presented in any article.

dom effect model was used to calculate the meta-analyses because the studies were classified as heterogeneous because they presented $I^2 > 50\%$ and $p < 0.10$. The meta-analyses showed a significant difference in blood glucose and serum triglyceride levels between the intervention group and the control group with a difference between the means of -49.97 [-57.18, -42.75] ($p < 0.00001$) and -63.54 [-106.98, -20.10] ($p = 0.004$), respectively. Regarding serum total cholesterol levels, the difference found between the means was -24.36 [-69.47, -20.75] ($p = 0.29$), being a non-significant value.

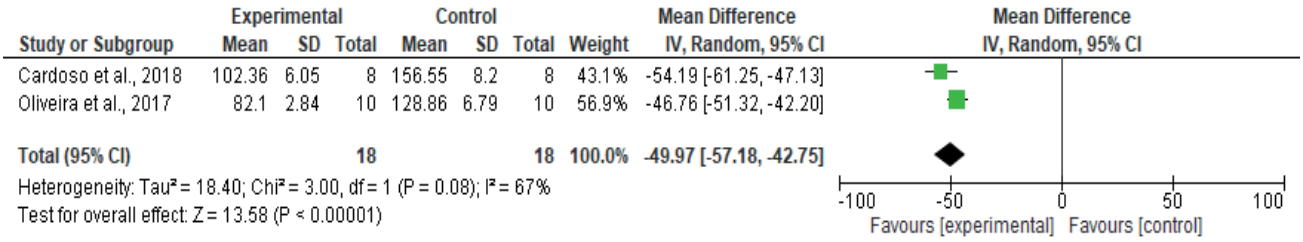

Figure 2. Meta-analysis of studies that evaluated the effect of *Eugenia uniflora* on blood glucose in rats with type 2 diabetes mellitus.

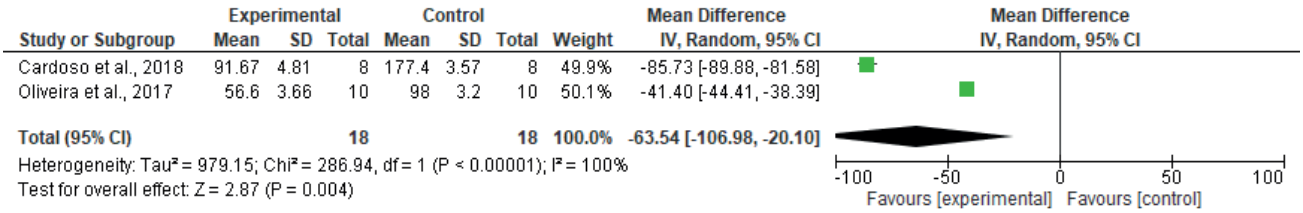

Figure 3. Meta-analysis of studies that evaluated the effect of *Eugenia uniflora* on serum triglyceride levels in rats with type 2 diabetes mellitus.

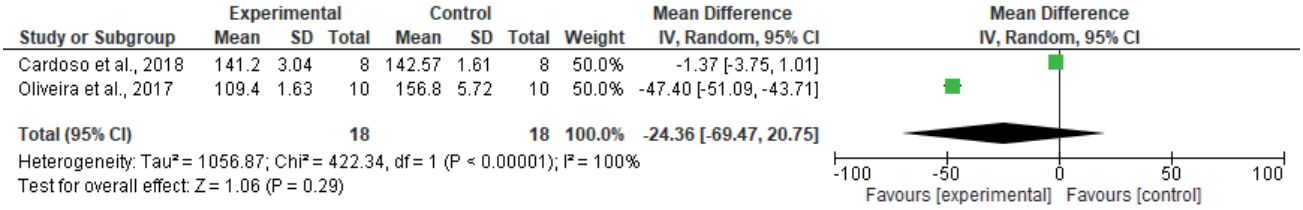

Figure 4. Meta-analysis of studies that evaluated the effect of *Eugenia uniflora* on serum total cholesterol levels in rats with type 2 diabetes mellitus.

DISCUSSION

In all *in vivo* preclinical trials included in the systematic review (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019), the use of *E. uniflora* promoted a decrease in serum glucose levels in rats with DM. The results of the meta-analysis confirmed the beneficial effect of *E. uniflora* in reducing blood glucose in rats with T2DM (Oliveira et al. 2017; Cardoso et al 2018).

One of the mechanisms that explains the hypoglycemic effect of these species is the inhibition of the activity of alpha-amylase and alpha-glucosidase digestive enzymes (Araujo et al. 2021). These enzymes are responsible for hydrolyzing carbohydrates in the digestive tract and, when inhibited, there is a delay in the absorption of glucose due to the decrease in the hydrolysis of carbohydrates. Thus, this mechanism is favorable because it helps to reduce postprandial hyperglycemia (Tundis et al. 2010; Rocha et al. 2019).

In one of the included preclinical studies, it was possible to observe a significant increase in the concentrations of serum insulin of rats with T1DM that received *E. uniflora* (Sobeh et al. 2019). A study conducted by Stanley and Kamalakkannan (2006) reported an increase in insulin concentrations in streptozotocin-induced diabetic rats after administration of rutin, which is a flavonoid. The increase in insulin release can be explained by the antioxidant action of the flavonoids present in these species, which are capable of scavenging free radicals. Thus, the oxidative stress caused in DM is prevented and, consequently, there is an increase in the release of the insulin hormone due to the protection of pancreatic beta cells (Coskun et al. 2004; Kamalakkannan e Prince 2006; Tsao 2010).

One of the main microvascular complications related to T1DM and T2DM is the diabetes kidney disease. This complication is caused due to high glucose levels that can cause damage in kidney cells and vessels. Thus, there is a decrease in the glomerular filtration rate and an increase in albuminuria (Amorim et al. 2019; Shigid and Karrar 2021). In a randomized controlled trial, patients with T2DM were randomly assigned to receive diet or hypoglycemic drugs (sulfonylureas, insulins or metformin) in order to monitor glycemic control. The improvement in glycemic control showed a decrease in the risk of microvascular complications in people with T2DM (Holman et al. 2008). Another study evaluated glycemic control in patients with T1DM and the results obtained were also satisfactory for the reduction of microvascular complications (Nathan et al. 2005). In view of the analyses, it is evident that glycemic control is essential for the reduction of microvascular complications in T1DM and T2DM. Among the studies selected in the present systematic review, the study that evaluated the diabetes kidney disease did not show significant reductions in urea levels after the use of *E. uniflora* (Oliveira et al. 2017).

The macrovascular complications are responsible for the main causes of mortality and morbidity in people with DM (Cole and Florez 2020). Among the hypotheses related to these complications are the high formation of AGEs and the increase in reactive oxygen species that are favored by hyperglycemia (Méndez et al. 2020). AGEs are the result of a non-enzymatic process known as glycation, which occurs when reducing sugars bind to proteins, nucleic acids and lipids (Faria and Persaud 2017). Receptors for AGEs are found in cells and, when they are activated, they can cause oxidative stress, chemotaxis and the release of pro-inflammatory cytokines that favor the development of macrovascular complications (Méndez et al. 2020). In addition, uncontrolled hyperglycemia causes the formation of reactive oxygen species (ROS) which overcome the antioxidant protection of cells, causing oxidative stress (Fatehi-Hassanabad 2010). ROS are produced in the body during cellular metabolism and exhibit high reactivity due to the presence of unpaired electrons that can cause cellular damage when reacting with DNA, lipids and proteins (Rendra et al. 2019). Excessive ROS formation also increases the risk of developing DM related complications (Volpe et al. 2018; Karadsheh et al. 2021).

Phenolic compounds are secondary metabolites produced by plants and are responsible for several biological activities such as antioxidant and anti-inflammatory action. Oxidative stress and inflammation are important factors for the onset of insulin resistance and for the development of T2DM2 (Keane et al. 2015). Flavonoids, phenolic acids and tannins are among the main classes representing polyphenols and this classification is made according to the chemical structure present (Stanley and Kamalakkannan 2006). All the articles included in the systematic review showed phenolic compounds as a chemical marker (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019). The presence of hydroxyls in phenolic compounds are responsible for their antioxidant and chelating activity. These compounds can repair free radicals and metal ions, in addition, they are responsible for inhibiting enzymes involved in the formation of ROS (Yahfoufi et al. 2018). The anti-inflammatory activity of phenolic compounds is related to the fact that they inhibit the cyclooxygenase and lipoxygenase pathways, in addition to preventing the biosynthesis of prostaglandin and tyrosine kinase enzymes. In addition, phenolic compounds can inhibit neutrophil and mast cell degranulation (Nijveldt et al. 2017). In an

in vivo study, the anti-inflammatory property of *E. uniflora* leaf extract was evaluated and it was observed that the extract prevented the formation of pro-inflammatory enzymes such as cyclooxygenases 1 and 2 and lipoxygenase (Sobeh et al. 2019).

The preclinical study that evaluated lipid peroxidation after using the plant showed significantly reduced levels in the intervention group compared to the control group (Sobeh et al. 2019). In DM, the increased formation of ROS can cause the oxidation of polyunsaturated fatty acids and thus lead to a dysfunction in the permeability and fluidity of cell membranes (Catalá 2006; Fatani et al. 2016; Karadsheh et al. 2021). Lipoperoxidation generates several secondary products, including malondialdehyde (MDA) which is used as a biomarker (Karadsheh et al. 2021). A study demonstrated the existence of a significant relationship between the amount of MDA and the levels of glycated hemoglobin (Hb1Ac), where T2DM patients with a higher percentage of HbA1c had higher levels of MDA (Fatani et al. 2016). Thus, the antioxidant and anti-inflammatory activities of *E. uniflora* may contribute to the reduction of glycemia, improvement of glycemic control, in addition to having the potential to promote the prevention and/or attenuation of microvascular and macrovascular complications related to DM (Schumacher et al. 2015; Sobeh et al. 2019; Araujo et al. 2021).

An important risk factor related to DM is the presence of cardiovascular diseases that can be prevented by controlling blood glucose, blood pressure and dyslipidemia (American Diabetes Association 2014; Cavan et al. 2016). In all preclinical studies that evaluated dyslipidemia, there was a significant reduction in triglyceride levels (Oliveira et al. 2017; Cardoso et al. 2018) and one showed a decrease in total cholesterol and LDL cholesterol (Oliveira et al. 2017). The result of the meta-analysis suggested the beneficial effect of *E. uniflora* in reducing serum triglyceride levels in rats with T2DM, however, no significant reduction in serum cholesterol levels was observed (Oliveira et al. 2017; Cardoso et al. 2018).

Dyslipidemia is common in T2DM and is characterized by a decrease in (high density lipoprotein (HDL) cholesterol levels and an increase in LDL cholesterol and triglycerides (Patti et al. 2019). In adipose tissue, the insulin resistance present in T2DM causes a decrease in the inhibition of the hormone-sensitive lipase enzyme and more free fatty acids are released into the bloodstream due to increased lipolysis (Hirano 2018). These excess free fatty acids are absorbed by the liver and form triglyceride-rich lipoproteins that are excessively secreted as very low density lipoprotein (VLDL) after packaging and are re-routed to adipose tissue (Reaven 2005; Hirano 2018). When VLDL loses triglycerides, it becomes intermediate density lipoprotein (IDL), which later gives rise to LDL (Meshkani and Adeli 2009; Nelson and Cox 2014). Excess adipose tissue releases inflammatory cytokines that are related to the development of insulin resistance in this tissue (Vilar et al. 2016; Kojta et al. 2020). Due to *E. uniflora* being rich in phenolic compounds, it has anti-inflammatory activity that can contribute to the improvement of insulin resistance in adipose tissue and collaborate to reduce triglyceride and LDL cholesterol levels and increase HDL cholesterol (Schumacher et al. 2015; Ricketts and Ferguson 2018; Ren et al. 2019; Fraga et al. 2019).

In the selected *in vivo* preclinical trials, the animals used were male Wistar rats (Oliveira et al. 2017; Cardoso et al. 2018; Sobeh et al. 2019) and only one also used Swiss albino mice (Sobeh et al. 2019). Dose concentrations of *E. uniflora* extracts ranged from 100 to 200 mg and the oral route of administration was chosen. The duration of each treatment was quite diverse, which may interfere with the results and contributed for the high heterogeneity between studies observed in the meta-analysis. In addition, other limitations consist of the part of the plant used, the chemical markers found, the type of DM evaluated and the method of inducing DM. Therefore, the results of the meta-analyses should be interpreted with caution, considering the number of studies included (only two) and the high heterogeneity between them.

Despite the variations present in the included studies, all showed a beneficial result in glycemic control after the administration of *E. uniflora*, indicating that this plant has a potential to be used as an adjuvant in the treatment of DM. On the other hand, the studies contained in the systematic review and meta-analysis had a low risk of bias and a high risk of bias, which indicates that the articles cannot be classified as of good quality according to the criteria of the SYRCLE scale, as they presented high risk of bias which can compromise its quality.

CONCLUSION

This systematic review allows to conclude that the species *E. uniflora* has a hypoglycemic action in rats with DM and the meta-analysis also suggested its effect in reducing serum glucose levels in rats with DM. Therefore, *E. uniflora* has great potential to assist in glycemic control in DM, in addition to being able to prevent complications related to DM, mainly due to its chemical composition, which is rich in phenolic compounds, which have antioxidant and anti-inflammatory properties. As few studies have been carried out to date evaluating the effect of *E. uniflora* in glycemic control

and prevention of DM complications, further studies are needed, mainly clinical trials, to validate the use of *E. uniflora* as an adjuvant in the treatment of DM in clinical practice.

AUTHOR'S CONTRIBUTIONS - Contributor Roles Taxonomy (CRediT):

Conceptualization, C.P.D. and R.O.C.; methodology, C.P.D., R.O.C. and A.S.M.; validation, C.P.D.; formal analysis, C.P.D., R.O.C. and A.S.M.; investigation, C.P.D., R.O.C. and A.S.M.; resources, C.P.D.; data curation, C.P.D., R.O.C. and A.S.M.; writing original draft preparation, A.S.M.; writing review and editing, C.P.D. and R.O.C.; visualization, A.S.M.; supervision, C.P.D.; project administration, C.P.D. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Appendix 1

Search strategy

The selection was performed using the descriptors “diabetes mellitus, type 2” and “diabetes mellitus, type 1” and their respective *entry terms* in combination with the descriptor “Eugenia” and its *entry terms*, using the “AND” connector between the terms. The definition of descriptors was done through the Medical Subject Headings (MeSH) as follow:

(“diabetes mellitus, type 2” or “Diabetes Mellitus, Noninsulin-Dependent” or “Diabetes Mellitus, Ketosis-Resistant” or “Diabetes Mellitus, Ketosis Resistant” or “Ketosis-Resistant Diabetes Mellitus” or “Diabetes Mellitus, Non Insulin Dependent” or “Diabetes Mellitus, Non-Insulin-Dependent” or “Non-Insulin-Dependent Diabetes Mellitus” or “Diabetes Mellitus, Stable” or “Stable Diabetes Mellitus” or “Diabetes Mellitus, Type II” or “NIDDM” or “Diabetes Mellitus, Noninsulin Dependent” or “Diabetes Mellitus, Maturity-Onset” or “Diabetes Mellitus, Maturity Onset” or “Maturity-Onset Diabetes Mellitus” or “Maturity Onset Diabetes Mellitus” or “MODY” or “Diabetes Mellitus, Slow-Onset” or “Diabetes Mellitus, Slow Onset” or “Slow-Onset Diabetes Mellitus” or “Type 2 Diabetes Mellitus” or “Noninsulin-Dependent Diabetes Mellitus” or “Noninsulin Dependent Diabetes Mellitus” or “Maturity-Onset Diabetes” or “Diabetes, Maturity-Onset” or “Maturity Onset Diabetes” or “Type 2 Diabetes” or “Diabetes, Type 2” or “Diabetes Mellitus, Adult-Onset” or “Adult-Onset Diabetes Mellitus” or “Diabetes Mellitus, Adult Onset” or “diabetes mellitus, type 1” or “Diabetes Mellitus, Insulin-Dependent” or “Diabetes Mellitus, Insulin Dependent” or “Insulin-Dependent Diabetes Mellitus” or “Diabetes Mellitus, Juvenile-Onset” or “Diabetes Mellitus, Juvenile Onset” or “Juvenile-Onset Diabetes Mellitus” or “IDDM” or “Juvenile-Onset Diabetes” or “Diabetes, Juvenile-Onset” or “Juvenile Onset Diabetes” or “Diabetes Mellitus, Sudden-Onset” or “Diabetes Mellitus, Sudden Onset” or “Sudden-Onset Diabetes Mellitus” or “Type 1 Diabetes Mellitus” or “Diabetes Mellitus, Insulin-Dependent, 1” or “Insulin-Dependent Diabetes Mellitus 1” or “Insulin Dependent Diabetes Mellitus 1” or “Type 1 Diabetes” or “Diabetes, Type 1” or “Diabetes Mellitus, Type I” or “Diabetes, Autoimmune” or “Autoimmune Diabetes” or “Diabetes Mellitus, Brittle” or “Brittle Diabetes Mellitus” or “Diabetes Mellitus, Ketosis-Prone” or “Diabetes Mellitus, Ketosis Prone” or “Ketosis-Prone Diabetes Mellitus”) and (“Eugenia” or “Eugenias” or “Euginia uniflora” or “Brazilian Cherry Tree” or “Brazilian Cherry Trees” or “Cherry Tree, Brazilian” or “Cherry Trees, Brazilian” or “Tree, Brazilian Cherry” or “Trees, Brazilian Cherry” or “Pitanga” or “Pitangas” or “Surinam Cherry Tree” or “Cherry Tree, Surinam” or “Cherry Trees, Surinam” or “Surinam Cherry Trees” or “Tree, Surinam Cherry” or “Trees, Surinam Cherry”).