Propolis extract supplementation in the complementary treatment of adults and elderly with Type 2 Diabetes Mellitus: a systematic review of clinical trial

Suplementação de extrato de própolis no tratamento complementar de adultos e idosos com Diabetes Mellitus Tipo 2: revisão sistemática de ensaios clínicos

DOI: 10.55905/oelv22n1-094

Recebimento dos originais: 01/12/2023
Aceitação para publicação: 02/01/2024

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ABSTRACT

Background & aims: bee products, such as propolis, have important natural properties to help reduce the risk of chronic noncommunicable diseases. Therefore, the objective of this review was to determine whether propolis intake helps to improve laboratory and anthropometrics indicators related to metabolic changes in type 2 Diabetes mellitus.  
Methods: systematic review of randomized clinical trials, published between 2000 and 2021, in Pubmed, Lilacs and SciELO databases, which indicated significant effects of propolis on laboratory indicators related to glycemic homeostasis, antioxidant and anti-inflammatory status. The articles were obtained according to the model recommended by PRISMA. After general analysis, protocols were used to assess the quality of evidence, using the Jadad scale, Consort and Cochrane.  
Results: glycemic homeostasis was evaluated using the following laboratory indicators: HOMA-IR, HOMA-β, fructosamine, fasting glucose and glycated hemoglobin. Significant changes in fasting glucose, 2-hour postprandial glucose were indicated in 71.43% of the studies. The antioxidant potential of propolis was evaluated in 71.43% of clinical trials. There was a significant reduction in pro-inflammatory cytokines, an increase in catalase activity and an increase in the antioxidant capacity of glutathione. The lipid profile was analyzed in 42.86% of the studies, indicating significant changes in total, LDL and HDL cholesterol.  
Conclusion: propolis can be considered an aggregating alternative for the conventional treatment of type 2 Diabetes mellitus. However, this food supplement is not a “miraculous” product, which eliminates the need for changes in lifestyle, including eating habits and regular physical activity, as well as the use of drugs, when necessary.  

Keywords: propolis, antioxidants, dietary supplement, diabetes mellitus.
prandial de 2 horas foram indicadas em 71,43% dos estudos. O potencial antioxidante da própolis foi avaliado em 71,43% dos ensaios clínicos. Houve uma redução significativa nas citocinas pró-inflamatórias, um aumento na atividade catalase e um aumento na capacidade antioxidante da glutatiana. O perfil lipídico foi analisado em 42,86% dos estudos, indicando alterações significativas no colesterol total, LDL e HDL. Conclusão: a própolis pode ser considerada uma alternativa agregadora para o tratamento convencional do Diabetes mellitus tipo 2. No entanto, este suplemento alimentar não é um produto "milagroso", o que elimina a necessidade de mudanças no estilo de vida, incluindo hábitos alimentares e atividade física regular, bem como o uso de drogas, quando necessário.

**Keywords:** própolis, antioxidantes, suplemento dietético, diabetes mellitus.

**1 INTRODUCTION**

According to the World Health Organization (WHO), by 2030, chronic non-communicable diseases (NCDs) will be responsible for more than 23 million deaths worldwide [1]. In Brazil, deaths caused by type 2 Diabetes mellitus (DM2) and other metabolic complications related to inadequate nutrition are the ones that most affect people over 30 years of age [2]. Therefore, changes in eating habits and regular physical activity are important interventions to treat and prevent the emergence of NCDs [3].

However, the limitations of conventional methods for the treatment of these diseases, and the high cost they represent for the health system, have contributed to the increased interest in the use of alternative therapeutic, since, generally, these methods seem indicate better adaptations, cases of obesity, DM2 and hypertension, in addition to being more accessible [4,5].

In this way, the use of natural products and their prominence in the scientific community increased. Plants and bee products have important natural properties, of high antioxidant potential, participating in the modulation of several physiological aspects of the organism, reducing oxidative stress and, therefore, the risks for the development of NCDs, being an aid, also, for their various treatment alternatives [6,7].

In this context, we have propolis, an ancient resinous substance, produced by bees (*Apis mellifera*), by collecting fragments of different plants. For this reason, there is a wide diversity of propolis in the world. The alternation in color, odor, texture and
chemical composition of propolis is directly associated with the phytogeography of the plant, where the resin is collected [8,9]. Thus, the phenolic compounds present in propolis extracts indicate a potential modulating effect on the immune system, in addition to an important antioxidant, antibacterial, anti-inflammatory and antitumor characteristic [5].

However, it seems necessary to systematize and evaluate these potential clinical outcomes obtained after the use of this supplement. This review, therefore, aims to evaluate the clinical effects attributed to different types of propolis, as well as their applicability, as aids in the treatment of DM2.

2 METHODS

This is a systematic review of clinical trials, published between 2000 and 2021. The searches were carried out in the following databases: US National Library of Medicine, Latin American and Caribbean Literature on Health Sciences and Scientific Electronic Library Online. The search terms used to select the articles were: propolis, brazilian propolis, diabetes, diabetes mellitus, DM2, obesity, insulin, insulin resistance, fat, metabolic syndrome, human, mice, rats and rabbit. The combinations between terms were articulated with the boolean operators AND, OR and NOT. All were obtained through Medical Subject Headings. The inclusion criteria considered articles in english, in the form of randomized clinical trials (parallel or crossover), that addressed the topic and answered the review questions, within the period used in the search, indicating the ingestion of the extract. of propolis. Studies had to assess laboratory tests, including those correlated with glycemic homeostasis, antioxidant activity, lipid profile and anthropometric indicators were also observed. In addition, after reading in full, articles that did not indicate a relationship with the proposed review were excluded.

Thus, the articles were selected in four stages, according to the model recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA): (1) identification of the articles obtained, through the search of the databases; (2) selection excluding articles that were not in the publication range, followed by screening by titles and abstracts; (3) eligibility assessed by reading the articles in full
(excluding those that did not meet the established inclusion criteria) and (4) inclusion of eligible articles in the systematic review [10].

The research results were organized through a database to analyze the evidence, including the following variables: article title and journal; randomization, blinding, placebo control or some other form of study control; sample number; genders; country where the study took place; average age or age group; proposed treatment; maintenance of standard diet and physical exercise; study duration; type of propolis used and significant results.

After a general analysis, the Jadad scale was used to assess the quality of the articles. The following indicators were considered: randomization, blinding and adequate execution during the study. The scale included three questions, with a score of “1” for “yes”, as well as two questions with the possibility of scoring an extra “1” later. This last phase indicated the possibility of reducing the score of the evaluated articles, when "no" was the answer [11].

The Consort (Consolidated Standards of Reporting Trials) was then used to reinforce the assessment of the quality of evidence. The protocol included three questions, where the first contained two questions that evaluated title and abstract, the second topic evaluated the introduction, through two questions, and the third topic consisted of eighteen questions, which analyzed methods, results and discussion, adding up to 22 questions, for each evidence assessed. All should be answered with "yes" or "no" and, at the end, all "yes" answers were added up and the percentage of affirmative answers was recorded [12].

The risk of bias analysis was performed using the Cochrane protocol. The tool was composed of some domains, used as guidelines, when questioning the evaluated evidence: random sequencing (1), allocation concealment (2), blinding of participants and professionals (3), blinding of outcome assessors (4), outcomes incomplete (5), selective outcome reporting (6), and other sources of bias (7). The opinion of each domain was made through three categories: high risk of bias (HRV), low risk of bias (LRV) and uncertain risk of bias (UVI) [13].
All analyzes in this review were conducted by two independently trained researchers. When in conflict, there was the inclusion of the opinion of a third trained researcher, to break the tie in the judgments of the data analysis. This systematic review was submitted to the International prospective register of systematic reviews (PROSPERO) CRD42022344813.

3 RESULTS

The flowchart was divided into four stages and 358 scientific articles were obtained in the identification, based on the search terms. A total of 283, which were unrelated to the review proposal, were excluded. After this step, 75 clinical trials were obtained, which could be in accordance with the proposal of the systematic review. In the selection phase, after reading the titles and abstracts, 68 articles were excluded, as they did not meet all the established inclusion criteria, and 7 articles went to the eligibility phase, in which the texts were read in full. The 7 clinical trials were eligible and therefore included in the review (Figure 1).

Figure 1. Flowchart of identification, selection, eligibility and inclusion of clinical trials in the systematic review.
3.1 GENERAL CHARACTERISTICS OF CLINICAL TRIALS INCLUDED IN THE REVIEW

According to the data presented in table 1, three types of propolis were used among the articles included in this review. Four studies (57.14%) evaluated the effects of propolis extract from Iran, two (28.57%) analyzed the effectiveness of brazilian green propolis and one study (14.29%) investigated the effects of propolis from Egypt. It is important to note that all studies using iranian propolis extract were carried out in Iran, as well as the study with egyptian propolis. On the other hand, the two articles with brazilian green propolis were offered in asian countries, one in Japan and the other in China.

The main exclusion criteria of the studies, during the participant selection stage, were: tobacco use, alcohol consumption, pregnancy, use of food supplements, consumption of foods with antioxidants, allergy to propolis, transplanted, cardiovascular diseases, ischemia, chronic kidney and liver dysfunction, as well as insulin users. In some of the studies, changes in diet or standard medication used to treat DM2 were also considered as exclusion criteria.

Data on the food consumption were collected from 24-hour recalls, with analysis on 3 or 5 days a week, through face-to-face interviews or phone calls. The information was compared between the control and intervention groups. As a result, in six articles (85.71%), patients were advised not to interrupt the standard medication procedure, not to change their diet and not to change their physical activity routine. Only the study carried out by El Sharkawy et al. (2016) [14] does not mention whether there was a recommendation to maintain these routine habits, especially regarding the use of hypoglycemic agents.

Body mass index (BMI) was the anthropometric indicator most used by the articles. Thus, based on the criteria established by the WHO, the volunteers had an average BMI between 25-29.9kg/m², considering 85.71% of the articles. Soon, the patients were diagnosed as being overweight. The study by Zakerkish et al. (2019) [15] was the only one in which participants indicated an average BMI equal to or greater than 30kg/m², therefore, according to the WHO, diagnosed with Obesity.
Complementary treatment with propolis lasted an average of 67 days. The study carried out by El Sharkawy et al. (2016) [14] had the longest period (6 months). While the sample number, considering all clinical trials, reached 466 volunteers, and the median was 62, regarding the number of participants, involving both genders, with ages ranging from 35 to 80 years. The average amount of propolis applied was approximately 918mg/day. Propolis-based supplementation was available in the form of capsules in five (71.43%) articles. In studies carried out by Fukuda et al. (2015) [16] and Samadi et al. (2017) [17], the propolis extract was offered in the form of tablets (Table 1).

The assessment of glycemic homeostasis was performed by comparing the results between the control and propolis-treated groups. The laboratory data were indicated in the analyzed evidence: HOMA-IR (homeostatic model assessment for insulin resistance), HOMA-β (homeostatic model assessment for the assessment of pancreatic beta cell function), Fructosamine, FBS (fasting blood sugar) and HbA1c (glycated hemoglobin). Significant changes in fasting glucose, two-hour postprandial glucose was indicated in 71.43% of the studies.

The antioxidant and anti-inflammatory potential, mainly attributed to phenolic substances, components of the propolis extract, was evaluated in 71.43% of the clinical trials included in this review. The articles indicated significant results regarding reductions in blood concentrations of pro-inflammatory cytokines, increase in catalase activity and increase in the antioxidant capacity of glutathione (GSH), after supplementation with propolis. The blood lipid profile of the patients, during the studies and at the end of the interventions, was analyzed in 42.86% of the trials. Significant results indicated changes in blood concentrations of total, low density lipoprotein (LDL) and high-density lipoprotein (HDL) between groups (Table 1).

3.2 LABORATORY INDICATORS AFTER TREATMENT WITH PROPOLIS EXTRACTS

3.2.1 Glycemic Homeostasis

The study by Zakerkish et al. (2019) [15] evaluated some important laboratory markers associated with glucose metabolism. This randomized, double-blind, placebo-
controlled clinical trial, published in Scientific Reports, selected 94 Iranian volunteers, diagnosed with DM2, receiving treatment with oral hypoglycemic agents. However, they did not use insulin, were male and female, aged between 35 and 85 years, separated into two groups: control and treatment with propolis. For eligible participants, there was a recommendation for daily ingestion of capsules containing 500mg of Iranian propolis extract, twice a day (12 in 12 hours), before meals, accompanied by a glass of water, for a period of 90 days. The propolis used in this study was collected from beehives in eastern Azerbaijan province during autumn. Although it had the same color, shape and dose, the supplementation given to the control group did not have the bioactive substances that were present in the propolis extract (intervention). The results indicated that blood concentrations of glycated hemoglobin (HbA1c), fasting insulin and glucose at 2 hours postprandial were significantly reduced in the treated group, compared to the control group (HbA1c: -8%, p = 0.006; fasting insulin: -28.6%; p < 0.0001) and (2 hours postprandial glucose: -50.8%; p < 0.0001). Homeostatic Model Assessment (HOMA-IR and HOMA-β) indicated a significant reduction of -46.6% and -45.8%, respectively, when compared between groups (p < 0.0001). Mean glycated hemoglobin decreased (HbA1c: from 8.65mg/dL ± 1.24 to 7.67mg/dL ± 1.27; p < 0.001) and there was a reduction in fasting insulin blood concentrations (from 14.03mg/dL ± 15.43 to 7.61mg/dL ± 6.69; p = 0.001), after using propolis from Iran. In addition, data from the control group indicated an increase (+32.93%) in glucose at 2 hours postprandial (from 168.05mg/dL ± 52.61 to 223.39mg/dL ± 82.04; p < 0.0001) at the end of the study. There was no significant difference for fasting glucose between the two groups (Table 1).

However, other clinical trials, which also used Iranian propolis extract as a complementary treatment for type 2 Diabetes mellitus, indicated favorable results for FBS, in addition to other laboratory indicators, which were observed by Zakerkish et al. (2019) [15]. Afsharpour et al. (2017) [18], through a randomized, double-blind, placebo-controlled study, selected 60 adult patients, aged between 30 and 50 years, of both genders, who did not present any change in medication in the last 2 months, did not use insulin and performed moderate physical activity. The treated volunteers had to ingest 500mg of Iranian propolis extract (capsules), three times a day, during meals, for 8 weeks.
The control group received similar capsules, but they were composed of wheat flour. After the intervention period, the authors indicated that blood concentrations of FBS were significantly reduced among patients treated with propolis (-19.8mg/dL ± 29.16; p < 0.01). The results also indicated a considerable reduction in blood glucose concentrations, postprandial 2 hour (-27.42mg/dL ± 44.5; p < 0.001), HOMA-IR (-1.08 ± 0.7; p < 0.04), HbA1c (-1.07mg/dL ± 1.6; p < 0.04) and fasting insulin (-1.65mg/dL ± 4.3; p < 0.03) in the treated group (Table 1).

Significant differences in relation to glucose metabolism indicators were also observed by Samadi et al. (2017) [17]. In this randomized, double-blind, placebo-controlled clinical trial, which followed the same inclusion criteria as in previous studies, 57 volunteers were divided into control and treated groups. The treated group received tablets containing 300mg of iranian propolis extract, to be consumed three times a day, one hour after each meal. The placebo group received the same supplement, but without the active ingredients of propolis.

At the end of 12 weeks, the blood concentrations of FBS and HbA1c reduced considerably in the treated group. On average, the reduction in fasting blood glucose was 17.76mg/dL in the group that ingested propolis, while the control group had an average increase of 6.48mg/dL. Changes in blood concentrations of glycated hemoglobin were like those of fasting glucose (Table 1). Hesami et al. (2019) [19], in a clinical trial that lasted 8 weeks, chose to evaluate the glycemic control of volunteers through fructosamine. However, the methods applied in the research are like those described in the study by Afsharpour et al. (2017) [18], including the daily dose of 1500mg of propolis extract from Iran, 3 times a day. At the end of the intervention, some significant results were obtained. The mean and initial blood concentration of fructosamine in the treated group was 391.19μmol ± 101.82, but after supplementation with propolis extract this value reduced to 336.477μmol ± 97.21 (p < 0.03). The initial mean value for fructosamine in the control group was 400μmol ± 87 and increased to 402.43μmol ± 103.75 at the end of the study (Table 1).

Unlike the other clinical trials cited, in the randomized, double-blind, placebo-controlled study by El Sharkawy et al. (2016) [14], the use of insulin as an exclusion
criterion was not considered, so 8% of the Egyptian volunteers were users of insulin and other hypoglycemic agents, for at least 6 months. In all, 50 patients (men and women) were considered eligible. Thus, for 182 days, the treated group received capsules with 400mg of Egyptian propolis extract, to be consumed once a day. Control group patients received placebo in identical vials. The results indicated that, at 3 and 6 months, mean blood concentrations of HbA1c in the propolis-treated group reduced by 0.82% and 0.96%, respectively, representing an improvement of between 13% and 16% in blood concentrations of glycated hemoglobin. The FBS also indicated a significant improvement in the group treated with propolis, after 3 and 6 months, in relation to the placebo group (p < 0.01) (Table 1).

In 2015, Fukuda et al. (2015) [16] conducted a survey with 80 volunteers of both genders in Japan. In this randomized, double-blind, placebo-controlled study, green propolis extract from Brazil was tested. Patients in the treated group received the supplement with a daily dose of 226.8mg for 56 days, while the control group received a placebo, made with safflower oil, wheat germ oil and perilla oil. Participants received guidance to follow a standard diet, already used in their routines, as well as were directed to maintain the physical exercise routine during the study period. Thus, after an 8-week intervention with Brazilian green propolis extract, the results on glucose metabolism, obtained through HOMA-IR, did not indicate significant differences for the two groups. However, the results of blood uric acid concentrations were highlighted, which increased significantly after 8 weeks in patients in the placebo group. The values remained close to the initial values in patients who supplemented propolis (p = 0.80). Furthermore, the estimate of Glomerular Filtration Rate (eGFR) indicated a considerable reduction in patients in the placebo group (p < 0.01). In the group that received propolis, the values remained like those at the beginning of the study, after 8 weeks (p = 0.52) (Table 1). Thus, corroborating the data analyzed by Zakerkish et al. (2019) [15], who also indicated a 20.7% reduction in the eGFR of the volunteers, from 114.31mL/minute ± 74.82 to 90.65mL/minute ± 25.87, in the placebo group, at the end of the intervention (p < 0.0001).
3.2.2 Lipid Profile

In total, three studies (42.86%) included in this review, analyzed the lipid profile of volunteers. After intervention with two daily doses of iranian propolis extract, Zakerkish et al. (2019) [15] indicated that the treated group evolved with an average increase in HDL of 10.6%, when compared to the control group (p = 0.024). On the last day, the treated group indicated an increase in HDL (9.5%), from 44.66mg/dL ± 8.69 to 48.91mg/dL ± 9.32 (p < 0.0001). However, the authors did not indicate significant differences for blood concentrations of total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG) and very low-density lipoprotein (VLDL) between groups (p > 0.05). The study carried out by Hesami et al. (2019) [19], who used one more dose of Iranian propolis extract (3 doses of 500mg, totaling 1500mg), indicated significant results for the reduction of oxidized LDL (Table 1).

The research carried out by Samadi et al. (2017) [17], who also used three daily doses, but with a lower amount of Iranian propolis extract (300mg in each tablet, totaling 900mg), indicated significant results in relation to CT. The propolis-treated group did not indicate significant differences for changes in TC concentrations. However, the placebo group indicated a considerable increase (p < 0.001). Therefore, the researchers rated the change in blood CT concentrations as a significant outcome (p = 0.010) (Table 1). Changes in blood LDL concentrations were like those found in CT. Furthermore, while the mean HDL in the treated group remained stable in the intervention period, it increased in the placebo group after the study period. These changes were not significant when the groups were compared (p = 0.020). Finally, they noted that there were no significant differences in blood concentrations of TG and VLDL between the two groups after the intervention.

3.2.3 Blood Biomarkers of Antioxidant and Anti-Inflammatory Status

Zhao et al. (2016) [20] developed a research whose objective was to analyze the anti-inflammatory potential and antioxidant capacity of phenolic compounds present in brazilian green propolis extract. A total of 65 chinese volunteers (men and women), aged between 35 and 78 years, were considered eligible for the survey. In this study, use of...
medication, including insulin, was one of the main exclusion criteria. The randomization of the control and treated groups was based on the fasting glucose information. The treated group received capsules with green propolis extract from Brazil, containing 900mg, to be consumed only once a day for 18 weeks. The standard diet, also known as the diabetic diet, was maintained throughout the research, as well as the regular practice of physical activity. At the end of the intervention, the authors observed a significant increase in serum glutathione (GSH) and total polyphenols in the group treated with brazilian green propolis extract, compared to the control group. Additionally, the results indicated significant reduction of serum carbonyls, lactate dehydrogenase (LDH) and tumor necrosis factor alpha (TNF-α). However, unexpectedly, there was an increase in interleukin 1β (IL-1β) and interleukin 6 (IL-6) in the treated group, indicating the following values: 22.0pg/mL ± 4.5 and 18.1pg/mL ± 5.0, respectively. This difference was more significant when compared to the values indicated in the control group: 18.7pg/mL ± 3.5 and 10.0pg/mL ± 5.0 (p < 0.05) (Table 1).

Although Fukuda et al. (2015) [16] have used brazilian green propolis extract, also, there were no significant results regarding blood concentrations of antioxidants and pro-inflammatory cytokines, after the 8-week intervention. However, the authors considered that the placebo group indicated a tendency towards an increase in TNF-α (p = 0.08), whereas in the group that received propolis the values indicated stability (Table 1).

The analysis of the anti-inflammatory potential of the iranian propolis extract was performed by Zakerkish et al. (2019) [15]. After the intervention period, the authors observed a significant reduction in blood concentrations of C-reactive protein (CRP), indicated in high sensitivity (hCRP), and a reduction in tumor necrosis factor alpha (TNF-α), of 60, 43% (p = 0.001) and 49.6%, respectively, when compared to the control group (p < 0.0001). However, iranian propolis did not indicate significant results for blood concentrations of IL-1β and IL-6, between groups. It is worth noting that on the last day of treatment there was a 16% reduction in blood IL-1β (34.84pg/mL ± 32.74 to 29.3pg/mL ± 25.66; p = 0.044), compared to the beginning of the study. In the end, the mean reduction in blood TNF-α concentrations in the group that received propolis was 30%
(122.98pg/mL ± 115.44 to 85.69pg/mL ± 84.7; p = 0.003). While in the placebo group there was an increase of approximately 53.7%, according to hCRP data (3925.92pg/mL ± 2546.47 to 6033.02pg/mL ± 2350.87; p = 0.007) and increase (12.4 %) in TNF-α (130.24pg/mL ± 11.99 to 146.41pg/mL ± 141.03; p < 0.001) (Table 1).

The context was similar in the study carried out by Afsharpour et al. (2017) [18], since the results also indicated a significant reduction in CRP and TNF-α, after treatment with three daily doses of 500mg of iranian propolis extract. The intervention group indicated a reduction of -2.5ng/mL ± 3.01 (p < 0.03) in relation to the CRP value and TNF-α decreased, approximately -2.67pg/mL ± 4.1 (p < 0.02). Furthermore, in the study by Hesami et al. (2019), who applied the same protocol, the results indicated a significant increase in catalase activity. At the beginning of the study, the group that received propolis indicated a mean concentration of 68.35U/mL ± 22.36, but the catalase function was potentiated to 83.06U/mL ± 27.37, after 56 days of treatment (p < 0.05). In contrast, in the placebo group, there was a reduction in this activity from 72.58U/mL ± 24.36 to 70.78U/mL ± 23.05 (Table 1).

Table 1. Clinical trials on the effects of propolis supplementation in volunteers with type 2 Diabetes mellitus

<table>
<thead>
<tr>
<th>Author et al. (Year)</th>
<th>Randomized? Blind? Controlled placebo?</th>
<th>Gender</th>
<th>Type of propolis</th>
<th>Country where it was performed</th>
<th>Duration (treatment)</th>
<th>What was the intervention (amount/day)?</th>
<th>n</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuda et al. (2015)</td>
<td>Yes / Yes / Yes</td>
<td>Man and Woman</td>
<td>Green (Brazil)</td>
<td>Japan</td>
<td>56 days</td>
<td>Brazilian green propolis extract in tablets (1 daily dose - 226.8mg)</td>
<td>80</td>
<td>Improvement of eGFR in T2DM patients after treatment with brazilian green propolis extract (p &lt; 0.01). Uric acid indicated similarity to the initial value of the study, in TG patients (p = 0.80). GP increased TNF-α (p = 0.08), as GT indicated stability (p = 0.98). Increase in serum GSH and total polyphenols in GT. Significant serum reduction of carbonyls, LDH and TNF-α in GT. However, there was an increase in IL-1β and IL-6 in GT (22.0 pg/mL ± 4.5 and 18.1 pg/mL ± 5.0). This difference was more significant than in the RG (18.7 ± 3.5 and 10.0 ± 5.0) (p &lt; 0.05).</td>
</tr>
<tr>
<td>Zhao et al. (2016)</td>
<td>Yes / No / No</td>
<td>Man and Woman</td>
<td>Green (Brazil)</td>
<td>China</td>
<td>126 days</td>
<td>Brazilian green propolis extract in capsule (1 daily dose - 900mg)</td>
<td>65</td>
<td>-------------</td>
</tr>
</tbody>
</table>
There was a decrease in serum levels of FBS in GT (-19.8 mg/dL ± 29.16) (p < 0.01). In addition, serum levels of 2hpp BS (-27.42 mg/dL ± 44.5) (p < 0.001), HOMA-IR (-1.08 ± 0.7) (p < 0.04), HbA1c (-1.07 ± 1.6) (p < 0.04) and fasting insulin (-1.65 mg/dL ± 4.3) (p < 0.03) were significantly reduced in GT. Significant reduction of CRP (-2.5 ng/mL ± 3.01ng/mL (p < 0.03) and TNF-α (-2.67 ng/mL ± 4.1) (p < 0.02) in GT.

Mean decrease of 17.76mg/dL in serum levels of FBS and HbA1c in GT. In addition, GT did not indicate a difference in TC levels, however, the Placebo Group (PG) indicated a considerable increase (p < 0.001). The changes in LDL levels were like those indicated in the GT.

HbA1c and 2hpp BS significantly decreased in GT compared to GP by 8% (p = 0.006), 28.6% (p < 0.0001) and 50.8% (p < 0.0001). HOMA-IR and HOMA-β indicated a decrease of 46.6% and 45.8% between the two groups (p < 0.0001). In the end, the mean reduction in GT was 0.98% in HbA1c (8.65% ± 1.24 to 7.67% ± 1.27) (p < 0.001) and 45% in fasting insulin levels (14.03 mg/dL ± 15.43 to 7.61 ± 6.69) (p = 0.001). Finally, there was a 20.7% decrease in eGFR, from 114.31 mL/min ± 74.82 to 90.65 mL/min ± 25.87 in the PG (p < 0.0001). Average HDL increase of 10.6% in GT. On the last day, the increase was 9.5% of HDL from 44.66 ± 8.69 to 48.91 ng/mL ± 9.32 (p < 0.0001). Finally, it decreased the serum levels of CRP and TNF-α, by 60.43% (p = 0.001) and 49.6% (p < 0.001) in GT, when compared to the GP (p < 0.0001). On the last day of treatment, there was a 20.7% reduction in serum IL-1β (34.84 pg/mL ± 32.74 to 29.3 pg/mL ± 25.66 pg/mL) (p = 0.04). The mean reduction in serum TNF-α in GT was 30% (122.98 ng/mL ± 115.44 to 85.69 pg/mL ± 84.7) (p = 0.003). While in the PG there was an increase of 53.7% (3925.92 pg/mL ± 2546.47 to 6033.02 pg/mL ± 2350.87) (p = 0.007) and a 12.4% increase in TNF-α (130.24 ng/mL ± 11.99 to 146.41 pg/mL ± 141.03) (p < 0.001).
<table>
<thead>
<tr>
<th>Study</th>
<th>Jadad Score</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesami et al. (2019)</td>
<td>Yes / Yes / Yes</td>
<td>Man and Woman Iranian Iranian propolis extract in capsules (500mg - 3 daily doses)</td>
</tr>
<tr>
<td>El Sharkawy et al. (2016)</td>
<td>Yes / Yes / Yes</td>
<td>Man and Woman Egyptian Egyptian propolis extract in capsule (400mg - 1 daily dose)</td>
</tr>
</tbody>
</table>

- **Reduction of fructosamine levels from 391.19 ± 101.82 to 336.47 ± 97.21 in GT (p < 0.03).** The GP indicated an increase from 400 ± 87 to 402.43 ± 103.75. There was a significant decrease in oxidized LDL at the end of treatment in GT. Enhanced catalase function in GT from 68.35 ± 2.32 U/mL to 83.06 ± 27.37 U/mL (p < 0.05).
- At 3 and 6 months of treatment, mean HbA1c levels decreased by 0.82% and 0.96%, respectively, from 8.71 ± 0.56% to 7.89 ± 0.43% and 7.75 ± 0.48% (p < 0.01). FBS had a significant improvement in GT compared to GP (p < 0.01).

**TC** – total cholesterol; eTFG – estimate of glomerular filtration rate; FBS - Fasting Blood Sugar = blood sugar test; GSH – Glutathione; GT – treated group; PG – placebo group; HOMA-IR – Test to assess insulin resistance; HOMA-β – Test to evaluate the activity of the pancreas; HbA1c - Glycated Hemoglobin Test; HDL - High density lipoprotein; IL-1β - Interleukin 1 beta; IL-6 - Interleukin 6; LDH - Lactate dehydrogenase; LDL - Low density lipoprotein; mg - milligrams; 2hpp BS = glucose 2 hours postprandial; CRP – C-reactive protein; TNF-α - Tumor necrosis factor-alpha; U/mL – units per milliliter, ng/mL – nanograms per milliliter, pg/mL – picogram per milliliter.

### 3.3 ASSESSMENT OF THE QUALITY OF SCIENTIFIC EVIDENCE INCLUDED IN THE REVIEW

The results, after evaluating the Jadad scale, regarding randomization, blinding and descriptions of loss of volunteers, indicated that in 42.86% of the studies there was a maximum score, ending with 5 points: Afsharpour et al. (2017) [18], Samadi et al. (2017) [17] and Hesami et al (2019) [19] (Figure 2A). Studies carried out by Fukuda et al. (2015) [16], El Sharkawy et al. (2016) [14] and Zakerkish et al (2019) [15] correspond to the percentage of 42.86%, but finished with 3 points (Figure 2A). Only the study by Zhao et al. (2016) [20] scored 1 (Figure 2A). Jadad scale was limited to detailing the randomization and blinding of the studies included in the review. Another protocol for evaluating the quality of the articles was demanded. Therefore, the Consort protocol was applied in the analysis of the evidence, in a more complete and judicious way, involving other structures of the text, such as title, abstract, introduction, methods, results and discussion.

The present systematic review considered only articles that indicated randomization. Therefore, the seven articles included were analyzed using the Consort protocol. The results indicated that two articles (28.57%) had 100% affirmative answers,
after completing the checklist: Afsharpour et al. (2017) [18] and Hesami et al. (2019) [19]. Two other studies reached a percentage above 90% for affirmative answers: El Sharkawy et al. (2016) [14] and Samadi et al. (2017) [17]. The study by Zakerkish et al. (2019) [15] reached the percentage of 86.36% in the checklist. Only Fukuda et al. (2015) [16] and Zhao et al. (2016) [20] indicated affirmative responses below 80%, so that the first indicated 77.27%, while the second indicated 72.72% (Figure 2B).

Figure 2C provides a comparative profile analysis of the quality ratings by Jadad scale and Consort protocol. The axes indicate that there was a misalignment between points C (Afsharpour et al., 2017) [18] and D (Samadi et al., 2017) [17] of the graph, indicating that the Consort protocol, by evaluating the information from the studies in greater detail, represents a more judicious judgment for quality.

The results of the analysis of the seven clinical trials, after evaluation by the Cochrane criteria, indicated 28.57% of the articles with more than 85% of responses for a “low risk of bias” (LRB): Afsharpour et al. (2017) [18] and Hesami et al. (2019) [19]. Another 57.14% of the studies indicated the percentage above 50% for LRB: Fukuda et al. (2015) [16], El Sharkawy et al. (2016) [14], Samadi et al. (2017) [17] and Zakerkish et al. (2019) [15]. Finally, only 14.29% had a percentage lower than 30%: Zhao et al. (2016) [20]. When analyzing the results, regarding the “high risk of bias” (HRB), only 28.57% of clinical trials scored above 10%, and 71.43% did not score. In addition, medians, involving the three categories of risk of bias, indicated a value of 57.14% in LRB, 0.0% in HRB and 42.86% in “uncertain risk of bias” (URB), which is another parameter indicating that the clear majority of studies are of relevant quality (Table 2).
Figure 2- A.t Score of scientific evidence according to the Jadad scale.

B - Assessment of scientific evidence according to the CONSORT protocol.

C - Comparative analysis of quality assessments by Jadad and Consort protocol.

Fonte: autoria propria
Table 2 – Assessment of the risk of bias of the studies by Cochrane

<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>LRB (%)</th>
<th>HRB (%)</th>
<th>URB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuda et al. (2015)</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>URB</td>
<td>LRB</td>
<td>LRB</td>
<td>HRB</td>
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<td>0</td>
<td>28,57</td>
</tr>
<tr>
<td>Zhao et al. (2016)</td>
<td>HRB</td>
<td>HRB</td>
<td>URB</td>
<td>URB</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>28,57</td>
<td>0</td>
<td>42,86</td>
</tr>
<tr>
<td>Afsharpoor et al. (2017)</td>
<td>LRB</td>
<td>LRB</td>
<td>LRB</td>
<td>LRB</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>85,71</td>
<td>0</td>
<td>14,29</td>
</tr>
<tr>
<td>Samadi et al. (2017)</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>URB</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>57,14</td>
<td>0</td>
<td>42,86</td>
</tr>
<tr>
<td>Zakerkish et al. (2019)</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>URB</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>57,14</td>
<td>0</td>
<td>42,86</td>
</tr>
<tr>
<td>Hesami et al. (2019)</td>
<td>LRB</td>
<td>LRB</td>
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<td>LRB</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>85,71</td>
<td>0</td>
<td>14,29</td>
</tr>
<tr>
<td>El Sharkawy et al. (2016)</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>URB</td>
<td>LRB</td>
<td>LRB</td>
<td>URB</td>
<td>57,14</td>
<td>0</td>
<td>42,86</td>
</tr>
</tbody>
</table>

Median: 57,14 0 42,86

LRB – low risk of bias; HRB – high risk of bias; URB – uncertain risk of bias.
Steps used by the Cochrane protocol: (1) random sequence; (2) allocation concealment; (3) blinding of participants and professionals; (4) blinding of outcome assessors; (5) incomplete outcomes; (6) selective outcome reporting; (7) other risks of bias.

Fonte: autoria própria

4 DISCUSSION

4.1 BODY MASS INDEX AND LABORATORY INDICATORS

After the grouping and analysis of the results, no significant effects of propolis were observed on the anthropometric indicators of the study volunteers. Although obesity is not the central point of investigation in this article, it is important to highlight this aspect, as there is a relevant association with DM2. This correlation is endorsed in this review, as six studies elected participants with DM2 and a BMI above 25kg/m², one of them above 30kg/m², indicating obesity. The results did not indicate statistical significance, considering the reduction in BMI, after treatments with propolis. However, some preclinical experimental studies, involving animals, have already indicated that propolis was able to reduce total body mass gain in mice and rats [21,22]

The results on laboratory indicators, correlated with glycemic homeostasis, indicated significant effects of propolis supplementation on fasting blood glucose, glycated hemoglobin (HbA1c) and 2-hour postprandial blood glucose. Improving fasting blood glucose and HbA1c is of great importance, as these two markers can prevent microvascular complications resulting from the worsening of DM2. Thus, glycemic control can minimize the risk of metabolic complications, which directly compromise
quality of life. Currently, cardiovascular problems are the main causes of morbidity and mortality in patients diagnosed with DM2 [23,24].

In addition, metabolic complications, involving changes in the blood vessels of patients, can compromise the functioning of the kidneys, since Diabetes mellitus is the main risk factor for Chronic Kidney Disease (CKD). In advanced circumstances, these disorders cause serious kidney damage, leading to progressive and irreversible loss of kidneys [25,26]. Although not evaluated in the studies included in this review, some laboratory indicators, such as proteinuria, albuminuria and uric acid are used to assess the risk of renal dysfunction, which may be related to DM2. In this sense, a study carried out by Silveira et al. (2019) [27], elected 32 participants, diagnosed with CKD, caused by Diabetes or other pathology. Volunteers received 500mg of brazilian green propolis extract, daily, for 52 weeks. The results, therefore, indicated that proteinuria was 30% lower among patients supplemented with green propolis from Brazil. In addition, a subgroup analysis was performed, which considered only patients with CKD, caused by caused by complications of Diabetes mellitus. The volunteers, supplemented with propolis, indicated a significant reduction in albuminuria. The authors highlighted that the reduction in proteinuria was independent of changes in laboratory glycemic indices throughout the treatment period. This statement directly corroborates the two articles in this review, which also used brazilian green propolis. Thus, it appears that this type of propolis has no significant relationship with glycemic control, but may be involved in antioxidant and anti-inflammatory modulation, involved in improving renal function [28, 29].

The cytokines TNF-α, IL-1β and IL-6 are known to participate in chronic inflammation and propolis is recognized as a natural product, consisting of bioactive compounds with antioxidant and anti-inflammatory properties. In this review, some studies legitimized the veracity of these effects, based on significant results on the reduction of pro-inflammatory cytokines TNF-α, IL-1β and IL-6, reduction of CRP, expressive increase of glutathione (GSH) and total polyphenols, in the groups treated with propolis extract. However, more attention should be paid to the results obtained in the study developed by Zhao et al. (2016) [20], because, contrary to what is expected from an anti-inflammatory supplement, the treated group indicated increased blood concentrations of IL-1β and IL-
6. This last-mentioned cytokine, however, appears in studies that indicate an antagonistic function to inflammation, inhibiting the production and secretion of IL-1β and TNF-α in the circulation [30,31].

A study by Gao et al. (2018) [32], who used Chinese propolis as a complementary treatment for patients diagnosed with DM2, for 18 weeks, indicated a significant increase in IL-6, as well as in blood GSH and total polyphenols, among patients supplemented with Chinese propolis. The results of this study corroborate those found in the study by Zhao et al. (2016) [20], indicated in this review, although the types of propolis are different and it was carried out as a quasi-randomized study [20,32].

In the same way that hyperglycemia favors inflammation, it can contribute to an increase in oxidative stress, stimulating the production of reactive oxygen species (ROS) [33,34]. The study carried out by Hesami et al. (2019) [19], present in this review, indicated that supplementation with Iranian propolis extract could potentiate the effects of the catalase enzyme, which participates in the decomposition of these oxidative and inflammatory molecules, which are increased in patients with type 2 Diabetes mellitus. Mujica et al. (2017) [35] performed a study that evaluated the effects of Chilean propolis extract on oxidative stress and lipid metabolism, in patients who had fasting glucose, altered lipid profile and blood pressure or Diabetes mellitus, cardiovascular disease and overweight. The results indicated an increase in blood GSH concentrations by 175%. According to the authors, the antioxidant property of propolis to reduce ROS may be associated with flavonoids, mainly caffeic acid phenethyl ester (CAPE) and quercetin. These compounds, which are abundant in almost all types of propolis, can activate factor 2-related erythroid nuclear factor 2 (Nrf2), which functions as an important antioxidant modulating protein, responsible for the potentiation of heme oxygenase-1 enzymes, phase II and enzymes linked to the metabolism of GSH, which improve the antioxidant capacity of cells. Furthermore, these flavonoids can inhibit the activation of the nuclear transcription factor NF-κB signaling pathway, confirming the results obtained by Gao et al. (2018) [32] and by the other articles [36,35,32].

The studies included in this review indicated that individuals treated with propolis had an improvement in the lipid profile from a significant increase in HDL and reduction
in oxidized LDL, in addition to an improvement in TC, although they did not find relevant results in relation to blood concentrations of TG and VLDL. Significant outcomes, in relation to blood concentrations of HDL, LDL and CT, are of great relevance about the risk of atherosclerotic diseases. In DM2, cases of dyslipidemia are directly associated with reduced blood concentrations of HDL, LDL and increased TG. Therefore, the modulation of the lipid profile, using propolis supplementation as an aid, could contribute to the reduction of cardiovascular risk [37].

It is important to point out some particularities presented by the studies, so that the beneficial effects attributed to propolis are well elucidated and are not misused in clinical practice. Regarding the indicators of glycemic homeostasis, it is noted that Fukuda et al. (2015) [16] and Zhao et al. (2016) [20] did not obtain significant results after supplementation with brazilian green propolis extract. On the other hand, the study by Zakerkish et al. (2019) [15] indicated effects of propolis on some glycemic markers, but not on fasting blood glucose concentrations. While El Sharkawy et al. (2016) [14], Samadi et al. (2017) [17] and Afsharpour et al. (2017) [18] presented the same and very expressive results in relation to blood concentrations of fasting glucose and other indicators of glycemic homeostasis. In addition, there are some differences between the results presented by the studies that evaluated the lipid profile. In general, these contradictions may have occurred due to the lack of standardization of the doses offered in the intervention; propolis of totally different botanical and geographical origin and, consequently, with different chemical and bioactive components; small number of participants (within the seven selected articles, the largest sample number was 94 volunteers); the nationality and food customs of each country; the age group, disregarding the physiological and metabolic particularities of the adult and the elderly and intervention time without an established pattern (studies with 8, 18 and up to 26 weeks).

4.2 LIMITATIONS OF THE METHODS USED IN THE STUDIES INCLUDED IN THE REVIEW

The form of presentation of the food supplement is an important limitation, since we have considerable physical and chemical differences between tablets and capsules,
especially about the speed of absorption, bioavailability and interactions that occur between the bioactive substance of the supplement and the nutrients of the foods, in addition to the influence of digestion enzymes. In view of this, pharmacologically, capsules have a certain advantage over tablets. Since, structurally, they are made of a protective gelatinous material that is easy to swallow, they preserve the internal content until it is released and then quickly absorbed in the intestine. On the other hand, tablets have a slower absorption time, as they are already disintegrated in the stomach (except for coated tablets), suffering the direct action of gastrointestinal fluids and digestive enzymes. As the tablets are powdered active ingredients, compacted in material that is usually starch or gum, there is a partial loss of the active content before reaching the intestine [38]. However, apparently, the factors involved in the process of releasing the active ingredients from the tablets and capsules had no influence on the effectiveness of the propolis supplement in the studies included in this review. Most studies opted for the use of capsules, which are generally tasteless, easy to swallow, and generally well accepted, especially by elderly patients.

In this sense, it is also worth noting that none of the studies in this review evaluated the microbiota. However, this assessment would be extremely relevant, given the essential role that the microbiota in intestinal homeostasis and in the health. Even changes in the composition of the microbiota have often been associated with increased risks of NCDs, such as Metabolic Syndrome, Obesity and type 2 Diabetes mellitus [39]. The microbiota of the volunteers, for example, could influence the number of phenolic compounds that were bioaccessible, after the tablets and capsules passed through digestion. Most of the polyphenols not absorbed in the small intestine could be metabolized by the intestinal microbiota, modulating the community of microorganisms present, thus inhibiting the action of pathogenic bacteria and metabolic impacts [40,39]. Another point of control of the methods, which was not indicated by most studies, is the number of bioactive compounds present in propolis, in each dose of the food supplement. Only the study carried out by Zakerkish et al. (2019) [15] described, in detail, each of these components. Providing this information, with the amounts of bioactive compounds
present in the types of propolis, would exemplify, in a more palpable and exact way, how standardized prescriptions could be developed in practice, ensuring better reproducibility.

In a complementary way, it is necessary to emphasize that none of the clinical trials proposed a role for propolis, as opposed to drugs already prescribed for the treatment of DM2, including hypoglycemic agents or compared to routine physical exercises and healthy eating. The authors were sensible in recommending the maintenance of all commonly used protocols and guidelines. The control of the food consumption of the volunteers, through the twenty-four-hour recalls, allowed a monitoring of the energy and nutrients consumed. This provided a better interpretation of the influence of the propolis extract on the body and its complementary clinical effects [41, 42].

It is also worth noting that studies evaluating the effects of propolis in humans are still very scarce. On the other hand, there is a profusion of scientific studies carried out in animal models. These studies are preclinical and may not indicate similarities when reproduced in human study models. Animal studies have their peculiarities, such as feed and/or gavage feeding, supplement overdoses, controlled environments, among others [43].

4.3 APPLICABILITY OF ANALYZED SCIENTIFIC RESULTS

The clarification of information based on scientific evidence is essential, as the propagation of information based on empiricism and the encouragement of the use of dietary supplements are increasingly common. Currently, social networks play an important role in the dissemination of information without scientific basis. Within this context, it is very common to overestimate food supplements and other so-called “miraculous” products, to the detriment of a balanced diet, based on in natura and minimally processed foods. It is even customary to face many manifestations of conflicts of interest and reductionist discourses, valuing “nutritionism” or “nutritional reductionism”, a term created by Australian researcher Gyorgy Scrinis [44].

With the advent of the Covid-19 pandemic, there has been an exponential increase in the demand for natural products and dietary supplements. Although several economic sectors have suffered the financial impacts resulting from social isolation, the supplement
trade was the one that suffered the least. The distribution and offer of the product in stores and pharmacies is immense. It is possible to find propolis in the form of capsules, alcoholic or aqueous solution, spray, paste, etc. However, according to the form in which it is made available, there is a considerable difference in the amount of propolis supplied per dose and, consequently, in the prices applied.

In view of this scenario, if we consider the median amount of propolis, in milligrams, most used by the scientific studies included in this review (900mg), it would be necessary to ingest at least seven capsules a day, to reach a few bioactive compounds related to potential health benefits. A bottle of this food supplement would last, on average, 8 days, that is, for a period of 30 days, you would need to purchase at least 4 bottles of propolis. It is important to reflect in this sense, as it can be a product that is not very accessible to most families, who survive in conditions of social and financial vulnerability. Linked to this factor, there is social inequality and high unemployment rates, which reduced access to healthy and adequate food in the Covid-19 pandemic. It is noted that these data were collected in a pre-pandemic context, but there was a significant worsening of this situation in the current economic scenario. Food supplements are complementary, in specific situations, when it is not possible to reach, through food, the necessary daily amounts of nutrients and bioactive substances. However, this is only possible when compatible financial conditions exist.

Finally, it is increasingly important, therefore, that researchers are close to the population, dialoguing and disseminating information, with scientific basis, on the effects of nutrients and bioactive substances, in the prevention and auxiliary treatment of chronic non-communicable diseases, like DM2. It is essential to emphasize that the change in lifestyle, with the adoption of a healthy and balanced diet, associated with regular practice of physical activity, are bases for the prevention and treatment of these diseases. Supplementation, as in the case of propolis, must always be rational and based on scientific evidence.
5 CONCLUSION

The present article indicated relevant results and discussions, for the proper elucidation of the beneficial effects, attributed to propolis, as a food supplement, to assist in the improvement of laboratory indicators, associated with glycemic homeostasis, antioxidant and anti-inflammatory profile of patients with DM2. Therefore, it can be considered an aggregating alternative for the conventional treatments of DM2. However, anthropometric indicators did not show significant results. It is important to consider that this food supplement is not a “miraculous” product, which eliminates the need for changes in lifestyle, including eating habits and regular physical activity, as well as the use of drugs when necessary. In addition, due to the reduced amount of scientific evidence, as well as the indications of possible heterogeneity of the analyzed variables and limited access to propolis from other countries, it is necessary that other clinical trials be developed, for further clarification of this potential benefit of the product. This will contribute to a more conscious, effective, safe, integrative, sustainable and accessible prescription, avoiding unnecessary expenses, also, with food supplements for the treatment of DM2.

AUTHOR CONTRIBUTIONS

Yuri Silva dos Santos: main author of the article, contributed to all stages of elaboration, data analysis and writing of the manuscript. Lucas Lombardo Borda: contributed to all stages of elaboration, data analysis and writing of the manuscript. Roberta Soares Casaes: contributed to the final writing of the manuscript. Alessandra da Silva Pereira: contributed to the final writing of the manuscript. Elaine Cristina de Souza Lima: manuscript supervisor, contributed to all stages of elaboration, data analysis and writing of the manuscript. Felipe de Souza Cardoso: manuscript supervisor, contributed to all stages of elaboration, data analysis and writing of the manuscript.
FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
REFERENCES


