

## **Kombucha: A systematic review and meta-analysis of experimental evidence of its effects on blood glucose, dyslipidemia and body weight in diabetes mellitus**

**Kombucha: uma revisão sistemática e metanálise de evidência experimental de seus efeitos na glicemia, dislipidemia e peso corporal no diabetes mellitus**

**Kombucha: una revisión sistemática y un metanálisis de la evidencia experimental de sus efectos sobre la glucosa en sangre, la dislipidemia y el peso corporal en la diabetes mellitus**

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### **Abstract**

Kombucha is a non-alcoholic fermented tea-based beverage produced by a symbiotic culture of bacteria and yeast. This growing popularity in the United States and developed countries has been part of the functional food's movement in the use of plant infusions as a promising alternative to the benefits of the microbiome in the treatment of obesity and diabetes. However, recent studies show controversial information about the effects of Kombucha on health, often driven by different theories leading to the empirical use of the drink without standardization of quantity and forms, and preparation, which can cause harm to human health. Given that, we carried out this systematic review to evaluate the effect of Kombucha on health through pre-clinical studies with scientific evidence available in the literature, to enable future studies in humans.

**Keywords:** Systematic review; Diabetes mellitus; Sugar-sweetened beverages; Functional food.

### **Resumo**

Kombucha é uma bebida fermentada não alcoólica à base de chá produzida por uma cultura simbiótica de bactérias e leveduras. Essa popularidade crescente nos Estados Unidos e países desenvolvidos vêm sendo parte do movimento de alimentos funcionais no uso de infusões de plantas como alternativa promissora nos benefícios do microbioma no tratamento da obesidade e diabetes. No entanto, estudos recentes mostram informações controversas sobre os efeitos da Kombucha na saúde, muitas vezes impulsionada por diferentes teorias acarretando o uso empírico da bebida sem padronização de quantidade e formas e preparo, podendo ocasionar prejuízos a saúde humana. Dado isso, realizamos esta revisão sistemática para avaliar o efeito da Kombucha na saúde através dos estudos pre-clínicos com evidência científica disponíveis na literatura, para possibilitar futuros estudos em humanos.

**Palavras-chave:** Revisão Sistemática; Diabetes mellitus; Bebidas adoçadas com açúcar; Alimento funcional.

## Resumen

La kombucha es una bebida a base de té fermentado sin alcohol producida por un cultivo simbiótico de bacterias y levaduras. Esta creciente popularidad en Estados Unidos y países desarrollados ha sido parte del movimiento de alimentos funcionales en el uso de infusiones de plantas como alternativa promisoría en los beneficios del microbioma en el tratamiento de la obesidad y la diabetes. Sin embargo, estudios recientes muestran informaciones controvertidas sobre los efectos de la Kombucha en la salud, muchas veces impulsada por diferentes teorías que conducen al uso empírico de la bebida sin estandarización de cantidad, formas y preparación, lo que puede causar daños a la salud humana. Dado eso, llevamos a cabo esta revisión sistemática para evaluar el efecto de Kombucha en la salud a través de estudios preclínicos con evidencia científica disponible en la literatura, para permitir futuros estudios en humanos.

**Palabras clave:** Revisión Sistemática; Diabetes mellitus; Bebidas azucaradas; Alimentos funcionales.

## 1. Introduction

Kombucha is the fastest growing product in the beverage market and one of the world's most popular low-alcohol fermented beverages (Kapp & Sumner 2019). In light of this, kombucha can be characterized as a bittersweet probiotic drink, produced from the fermentation of black tea or sweetened green tea, with a symbiotic culture of acetic acid bacteria and yeast with bacteria (Dimidi et al. 2019).

The kombucha drink originates from an infusion which consists of two essential ingredients: a) black tea or green tea with added sugar and b) biofilm, a symbiotic culture of bacteria and yeast, with an estimated fermentation time of seven to ten days (Martínez Leal et al. 2018). It is encouraged to be taken manually and without a standard dose to assist in the treatment of diabetes mellitus (DM).

According to Saklayen (2018), DM is currently one of the most common chronic diseases, and it affects more than 425 million people worldwide with a predicted rise to 642 million cases by 2040 (Saklayen 2018). Specifically in Brazil, this pathology affects around 7.7 million people aged 20 to 79 years who have not yet been diagnosed, representing approximately 46.0% of the Brazilian population (Grotta et al. 2021). Type 2 diabetes (DM2), which is considered to be the most common cause in approximately 90% of DM cases, accounts for a total of 4 million deaths a year caused by either the disease itself or its complications (American Diabetes Association 2014; Turner et al. 1996). It is also regarded as a major cause of morbidity and mortality rates (Ruiz-Ramos et al. 2006); as a consequence, it was recognized by the World Health Organization (WHO) as one of the four major Noncommunicable Chronic Diseases and the third largest risk factor of premature mortality resulting from hyperglycemia worldwide (Oliveira et al. 2017; Marinho et al. 2021); Although kombucha is consumed by humans, two previous systematic reviews have been published on Kombucha (Kapp & Sumner 2019; Ernst 2003). Ernst (Ernst 2003) and Kapp & Sumner (Kapp & Sumner 2019), respectively, researching studies of the influence of kombucha on human health in different studies including possible non-human research studies. The results found in all benefits, with such studies contradicting these benefits and limiting the designs of study. Clinical data, clinical trials- whether to conduct clinical studies or animal studies to respond to the health of the real of kombucha in health or human health screenings.(Kapp & Sumner 2019)

This study is justified by the fact that most studies still only involve experiments with animals, predominantly rats. In view of the fact that studies on the effects of kombucha on blood glucose, dyslipidemia and body weight have been inconclusive, this study seeks to employ systematic review (SR) and a meta-analysis to determine the effects of kombucha on rats with diabetes, to make a contribution to the research carried out previously and establish the degree of consonance or dissonance with such previous studies.

## 2. Objective

To verify the effects of Kombucha on blood glucose, dyslipidemia and body weight in rats with diabetes.

## 3. Methods

### Study model

Systematic review of studies of interventions - Cochrane Handbook for Systematic Reviews of Interventions version 5.1. The study was registered on the OpenScience Framework platform (<https://osf.io/wn762>) with the following registration number: DOI: 10.17605/OSF.IO/3U7GF.

### Purpose of the study

The initial search strategy included primary databases that concentrated on original scientific articles, theses, dissertations, abstracts, among other research activities, including five databases (PubMed, SCOPUS, Web of Science, LILACS, Cochrane Central Register of Controlled Trials) directly related to health, which led to a better control and reduced the risk of selection bias (Song et al. 2000).

### Databases and Search Strategy

The MeSH descriptors were searched for "kombucha", "tea fungus", "kombucha tea", and the terms "kombucha tea" and "camelia sinensis" were found. In Medline, we found the terms: "tea fungus", "kombucha", "kampuchea tea", "fungus metabolites", "fermented tea" and "health benefits". The last term was removed from the strategy, since a small number of articles was found when this term was included. Therefore, the strategy used for this study was based on: "kombucha tea" OR ("camelia sinensis" AND "fermented tea") OR ("fungus metabolites" AND kombucha) OR (kombucha AND "tea fungus") OR "kampuchea tea" OR kombucha.

The systematic search was performed from May 11, 2017 to September 30, 2019 and followed the search strategy outlined above, together with the PubMed (Medline), Web of Science (Science and Social Science Citation Index) databases, the Latin American and Caribbean Center on Health Sciences Information (LILACS), Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the search for unpublished or unindexed studies in the literature, (the gray area of literature), was carried out with the aid of Google Scholar (<http://scholar.google.com/>), the Gray Literature Report from the New York Academy of Medicine (<http://www.greylit.org/>), and the World Health Organization - WHO (<http://www.who.int/>). In addition, checks were made in the clinical trial registry, including the Trials Central (<http://www.trialscentral.org/>) and ClinicalTrials.gov (<https://clinicaltrials.gov/>). A full search strategy is provided in Frame 1.

**Frame 1:** Search strategy according to the correspondent database.

DATABASE	Search Strategy
The Cochrane Central Register of Controlled Trials (CENTRAL)	#1: MeSH descriptor: [Kombucha] explode all trees. #2: MeSH descriptor: [tea fungus] explode all trees. #3: MeSH descriptor: [Kombucha tea] explode all trees. #4: #1 AND #2 AND #3
PubMed (Medline)	#1: "tea fungus" #2: "Kombucha" #3: "kampuchea tea" #4: "fungus metabolites" #5: "fermented tea" #6: "health benefits" #7: #1 AND #2 AND #3 AND #4 AND #5
EMBASE	#1: "Kombucha tea" OR ("camelia sinensis" AND "fermented tea") OR ("fungus metabolites" AND Kombucha) OR (Kombucha AND "tea fungus") OR "kampuchea tea" OR Kombucha
The Latin American and Caribbean Centre on Health Sciences Information (LILACS/Bireme)	#1: mh: "Kombucha tea" OR ("camelia sinensis" AND "fermented tea") OR ("fungus metabolites" AND Kombucha) OR (Kombucha AND "tea fungus") OR (kampuchea tea) OR (Kombucha) OR (Chá de Kombucha) OR (Té de Kombucha) OR (Thé kombucha) OR (mh: D20.215.784.844.500) OR (mh: G07.203.100.831.500) OR (mh: G07.203.200.625) OR (mh: J02.200.831.500) OR (mh: J02.350.625)
SciElo e Scopus (Elsevier)	#1: "Kombucha tea" OR ("camelia sinensis" AND "fermented tea") OR ("fungus metabolites" AND Kombucha) OR (Kombucha AND "tea fungus") OR "kampuchea tea" OR Kombucha
Web of Science (Clarivate Analytics)	#1: "Kombucha tea" OR ("camelia sinensis" AND "fermented tea") OR ("fungus metabolites" AND Kombucha) OR (Kombucha AND "tea fungus") OR "kampuchea tea" OR Kombucha

Source: Authors.

In conducting the analysis of the articles that formed a part of this SR, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)(Moher et al. 2009) while the research question that was defined followed the PICO (Participants, Intervention, Comparison, and Outcomes) strategy, systematizing the search for randomized controlled studies that used Kombucha in rats with diabetes, fed a standard diet and water, given the largest number of studies available to standardize the search methodology. There was no limitation regarding the date of publication of the article or the language.

### Data Selection and Analysis

The titles and abstracts of all the articles identified by the search strategy, were independently assessed by two researchers. All the abstracts that did not provide sufficient information on the inclusion and exclusion criteria, were selected for a full-text evaluation report.

In the second phase, the same reviewers independently assessed the full-texts of the articles and made the selection in accordance with the eligibility criteria. The stages of the search and selection of articles were as follows. The results of each search were recorded and documented to ensure their reproducibility. The following information was collected for each electronic search that was carried out: database identification, email server address, month and year of the search and the search strategy employed.

After the initial screening of the references found in the databases, the abstracts were read and analyzed for selection on the basis of the eligibility criteria. If the abstracts were unclear with regard to their content, we read the studies in full, while taking account of the need to observe the applied methods and understand the findings. For a more careful screening, we decided to select publications that were the most complete and the ones that best met the desired criteria for inclusion in case of duplicity or double standards, as well as those that had been subjected to repeated analysis and published in other formats with similar findings and were based on the same research.

### **Eligibility criteria and selection of articles**

Therapeutic studies on kombucha in rats were included. However, the following were excluded: studies involving other animals such as pigs, birds and mice; studies linking kombucha with alternative treatments; observational studies; case studies; *in vitro* studies and clinical trials involving humans.

### **Process of extracting data from the jobs that were included**

Data were only extracted from sources which had methodological validation, that is, those conducted and analyzed by one evaluator and later by another. In addition to the findings, there was information about the features of the research and its methods; the population or study sample; the size of this sample; its composition; the frequency of use of kombucha; the therapeutic benefits of this drink; the period of use; the place of origin of the study (i.e., city, state, country); location where the research was conducted; name of the main author and date of publication.

### **A risk assessment of bias**

The risk of bias was assessed by the SYRCLE tool, created from the Cochrane Risk-of-Bias Tool (RoB), and adjusted to bias factors that play a key role in animal intervention studies. The items that make up the SYRCLE tool include the evaluation of selection bias, performance bias, detection bias, friction bias, report bias and other biases (Hooijmans et al. 2014).

### **Statistical analysis**

A random effects model was used for the meta-analysis, which can be regarded as the effect measure for the standardized mean difference.  $I^2$  and Cochran's Q test were calculated to assess the degree of heterogeneity between the studies, with a significance of  $P < 0.05$ . The results were visualized by means of the forest plot graph for triglyceride and high-density lipoprotein (HDL) outcomes. The whole data analysis was performed using the statistical software - R Core Team (R Core Team 2018) (Vienna, Austria) with the aid of the metafor package (Viechtbauer 2010; Martínez Leal et al. 2018).

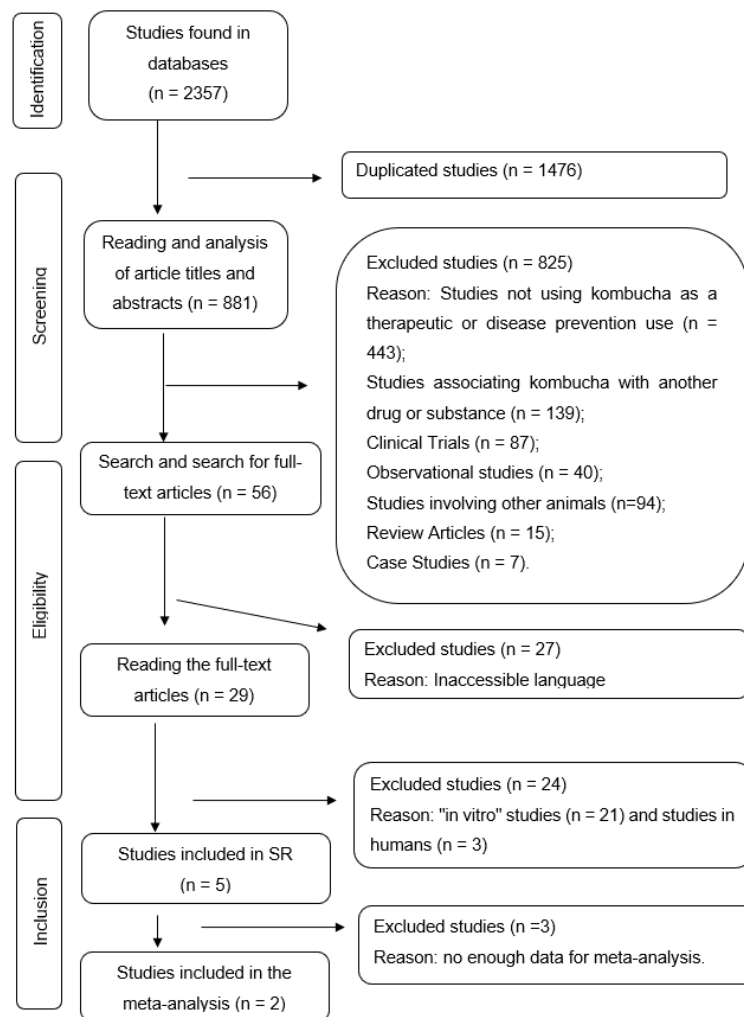
## 4. Results

### Selected studies

In the course of search, a total of 2357 articles were found. Of these, 1476 were rejected because they had duplicate databases, leaving 881 for analysis. A further 852 articles were rejected after being subjected to exclusion criteria, which left 29 articles that were selected for full reading. A further 21 *in vitro* studies and 3 human studies were rejected, on the basis of the inclusion and exclusion criteria. As a result, this left five studies included for SR, and of these, two studies were included for meta-analysis. (Figure 1).

**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram of study selection.

Source: Author.



Source: Authors.

There were five studies which stated that consumption of kombucha prepared with green tea significantly reduced blood glucose and lipid parameters, low-density lipoprotein cholesterol (LDL-c), total cholesterol and triglycerides, with increased high-density lipoprotein cholesterol (HDL-c). In addition, some studies found signs of weight reduction in the green tea and kombucha group and a potential antihyperglycemic effect relative to the control group. The risk of bias assessment was carried out in accordance with the Cochrane Bias Risk Tool (RoB)(Sterne et al. 2019; Saklayen 2018) for the six animal studies described in SYRCLE (Table 1)

**Table 1.** SYRCLE Tool for Assessing the Risk of Bias between Studies.

<b>Study/Year</b>	<b>Was the allocation sequence adequately generated and applied?</b>	<b>Were the groups similar at baseline or were they adjusted for confounders in the analysis?</b>	<b>Was the allocation to the different groups adequately concealed during?</b>	<b>Were the animals randomly housed during the experiment?</b>	<b>Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?</b>	<b>Were animals selected at random for outcome assessment?</b>	<b>Was the outcome assessor blinded?</b>	<b>Were incomplete outcome data adequately addressed?</b>	<b>Are reports of the study free of selective outcome reporting?</b>	<b>Was the study apparently free of other problems that could result in high risk of bias?</b>
<b>Hosseini <i>et al.</i>, 2016<sup>15</sup></b>	No	Yes	No	No	No	No	No	No	No	No
<b>Hosseini <i>et al.</i>, 2015<sup>17</sup></b>	No	Yes	No	No	No	No	No	No	No	No
<b>Bhattacharya <i>et al.</i>, 2013<sup>16</sup></b>	No	Yes	No	Yes	No	No	No	No	No	No
<b>Srihari <i>et al.</i>, 2013<sup>18</sup></b>	No	Yes	No	Yes	No	No	No	No	Yes	No
<b>Dashti <i>et al.</i>, 2000<sup>19</sup></b>	No	Yes	No	No	No	No	No	No	Yes	No

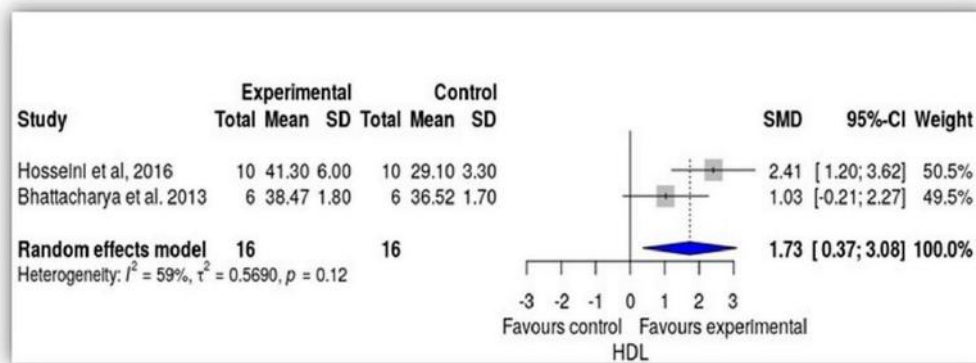
The additional signaling questions are included to assist judgment. “Yes” indicates low risk of bias; “no” indicates high risk of bias; and “unclear” indicates an unclear risk of bias. If one of the relevant signaling questions is answered with “no,” this indicates high risk of bias for that specific entry. Source: Authors.

### Meta-analysis

Studies by Hosseini et al. (Hosseini et al. 2016; American Diabetes Association 2014) and Bhattacharya et al. (Bhattacharya et al. 2013; Turner et al. 1996) that describe the effects of kombucha on HDL-c and blood glucose levels, were included in the meta-analysis. In their summary of the meta-analysis, they calculated a measure that significantly favors the increase of HDL-c.

With regard to the effect of kombucha on HDL-c, the forest plot graph (Figure 2) shows a greater increase in HDL-c levels compared with the control group (Effect Size = 1.73 (95% CI 0.37; In addition, the value of P = 0.12 showed that the studies are uniform. It should also be noted that the study by Hosseini et al. (Hosseini et al. 2016; American Diabetes Association 2014) makes the greatest contribution to the summary measure, as it has the largest sample size compared with the study by Bhattacharya. (Bhattacharya et al. 2013; Turner et al. 1996)

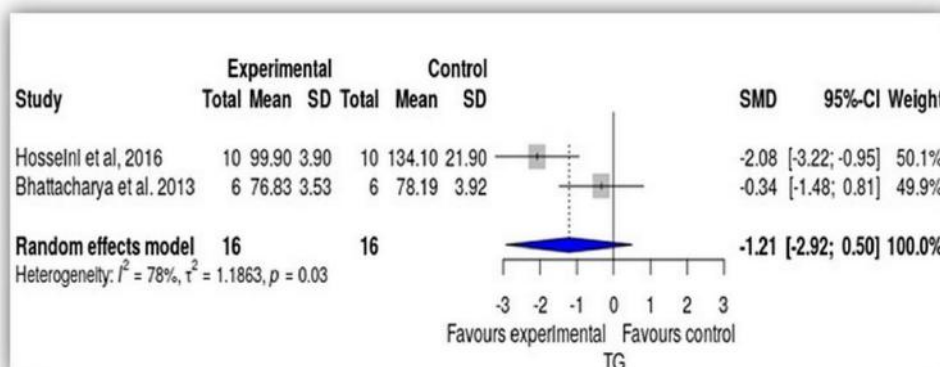
**Figure. 2.** Heterogeneous measurements for a profile of high-density lipoprotein cholesterol (HDL-c), Forest Plot graph where inconsistency test ( $I^2$ ): 62.32%, Q(degree of freedom= 1) = 4.7146, p-val = 0.1033.



Source: Authors.

As for the effect of kombucha on triglyceride (TG) levels, the forest plot graph (Figure 3) does not show any significant difference when compared with the control group, since the diamond shape crosses the vertical line (Effect Size = -1.21 ((95% CI -2.92; 0.50)). However, the value of P = 0.03 demonstrates that the studies are heterogeneous. It is clear that, as in the previous graph, the study by Hosseini et al. (Hosseini et al. 2016) makes a greater contribution to the summary measure.

**Figure. 3.** Heterogeneous measurements for a profile of triglycerides, including a Forest Plot graph where inconsistency test ( $I^2$ ): 78.79%, Q(degree of freedom= 1) = 4.7146, p-val = 0.0299.



Source: Authors.



Thus, the study by Hosseini et al, 2016(Hosseini et al. 2015) has the largest contribution to the summary measure, as it has a larger sample size than the study by Bhattacharya et al.(Bhattacharya et al. 2013) Consumption of kombucha prepared with green tea leads to the reduction of triglycerides, and reduces the serum HDL-c level in comparison with the control.

All studies are summarized in Table 2.

**Table 2.** Summaries of studies included in the systematic review.

Reference	Country	Study type	Species	Method	Intervention Group	Control Group	Studied variables	Results
Hosseini, <i>et al.</i> , 2016 <sup>15</sup>	India	Experimental	Rats	(n=50) Study conducted with 50 diabetic rats (male) weighing 200-220g randomized into 5 groups: control group (water); group receiving black tea; Green Tea; Kombucha prepared with black tea; Kombucha prepared with green tea.	(n=40) Daily administration of 5 mL/kg for 4 weeks in groups 5 (n=10), group 4 (n=10), group 3 (n=10) and group 2 (n=10).	(n=10) Group 1 = Water	Blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), triglycerides (TG) and total cholesterol.	Significant reduction in blood glucose, LDL-c, total cholesterol and triglycerides with an increase in HDL-c, in Kombucha group, prepared with green tea.
Hosseini, <i>et al.</i> , 2015 <sup>17</sup>	India	Experimental	Rats	(n=30) Study with rats diabetes induced by alloxan, weighing 200g-220g, divided into a control group; green tea group and green tea Kombucha group for 4 weeks.	(n=20) Received green tea (n=10) and Kombucha prepared from green tea (n=10) and 5 ml/kg of water per day for four weeks.	(n=10) Group 1 = Water	Body weight	Weight reduction in green tea and Kombucha group.
Bhattacharya, <i>et al.</i> , 2013 <sup>16</sup>	Spain	Experimental	Rats	(n=36) Kombucha and black tea were offered to alloxan-induced diabetic rats (Swiss) albino male rats, weighing 180-200 g for 14 days. The animals were divided into six groups with six rats each.	(n=30) Group 2 (n=6): normal rats that received Kombucha at a dose of 150 mg of lyophilized extract (Lex) per kg of body weight. Group 3 (n=6): alloxan diabetic rats. Group 4 (n=6): rats received Kombucha at a dose of 150 mg of LEX / kg of body weight. Group 5 (n=6): rats received black tea at a dose of 150 mg LEX / kg body weight.	(n=6) Group 1 = Water	Weight, plasma insulin, blood glucose, glycated hemoglobin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, urea, total cholesterol, high density lipoprotein (HDL) and triglycerides (TG)	Potential effects of black tea Kombucha in improving blood glucose and restoring the pathophysiological changes in alloxan-induced diabetes.

					Group 6 (n=6): rats received glibenclamide at a dose of 1 mg/kg.			
Srihari, <i>et al.</i> , 2013 <sup>18</sup>	Netherlands	Experimental	Rats	(n=36) Were analysed male rats with diabetes induced by 45mg/kg streptozotocin, body weight in 180-220g. The rats were divided into 6 groups with 6 animals each with oral administration of Kombucha black tea through a gastric tube, for 45 days.	(n=30) Group 2 (n=6): rats without diabetes, receiving Kombucha ad libitum, Group 3 (n=6): controlled diabetes group; Group 4 (n=6): Diabetic rats receiving Kombucha (3 mg/kg). Group 5 (n=6): Diabetic rats receiving Kombucha (6 mg/kg). Group 6 (n=6): Diabetic rats receiving Kombucha (12 mg/kg).	(n=6) Group 1 = No intervention and no diabetes induction	Blood glucose, insulin, glycosylated hemoglobin (HbA1c); total hemoglobin and glycogen histological analysis; glucose-6-phosphatase, fructose-1,6-bisphosphatase and hexokinase.	Hypoglycemic effects associated with the use of black tea Kombucha in diabetic rats.
Dashti, <i>et al.</i> , 2000 <sup>19</sup>	Turkey	Experimental	Rats	(n=15) Study with male rats (body weight between 180g-220g) with diabetes induced by intraperitoneal injection of streptozotocin (60mg/kg), in free access to the normal diet, at a temperature of 22-25°C, divided equally into three groups.	(n=10) Group 1 (n=5) consumed black tea and group 2 (n=5), Kombucha prepared with black tea.	(n=5) Group 1 = Water	Blood glucose	The blood glucose of rats that consumed Kombucha with black tea was significantly reduced.

Source: Authors.

## 5. Discussion

The results of this SR and meta-analysis show that kombucha leads to an increase of HDL-c levels in diabetic rats. With regard to the SR, five experimental studies were included in diabetic rats (Bhattacharya et al. 2013; Dashti & Morshedi 2000; Hosseini et al. 2015, 2016; Srihari et al. 2013) and the SYRCLE method was used to assess the risk of bias in animal studies.

The results were described for all the outcomes (even those for which there was no significant difference), and other biases were found. Most of the five studies answered the SYRCLE questions (Hooijmans et al. 2014). There was a “high risk of bias”, except for the questions: “Were the groups similar at the baseline, with regard to factors such as gender, weight and age?”. “Was there a low risk of bias?”. However, it was found that, in the study by Srihari et al., (Srihari et al. 2013) there was a low risk of bias for the method of dividing animals into groups, as well as for the method of separating them into groups, so that the animals could be given the appropriate medication. Their findings were described for the outcomes, even for those in which there was no significant difference. This method differs from the one used in the study by Bhattacharya et al. (Bhattacharya et al. 2013) in so far as there is a low risk in the method of allocating animals to the groups, and from the method used in the study by Dashti et al., (Dashti & Morshedi 2000) since it poses a low risk; the results were described for all the outcomes, even for those in which there was no significant difference.

The experimental methodology in use differs in some studies, as some administered kombucha after it had been fermented from green tea or black tea as a base drink. In addition, some used Streptozotocin or alloxan in rats as an induction of diabetes. The diabetogenic mechanism of alloxan is mediated by reactive oxygen species (Hosseini et al. 2016). The product of its reduction, (dialuric acid), establishes a redox cycle through the formation of superoxide radicals, which then undergoes dismutation to hydrogen peroxide, and causes the rapid destruction of pancreatic  $\beta$ -cells (Hosseini et al. 2016; Srihari et al. 2013). Rats whose diabetes was induced by alloxan, which is toxic to  $\beta$ -pancreatic cells, were given kombucha. There were significant results, shown by the lowering effect on the potential blood glucose, as reported in the study by Hosseini et al (Hosseini et al. 2016).

There were also positive results in a hypoglycemic effect and evidence of how kombucha could control diabetes, as shown by Srihari et al. (Srihari et al. 2013) in their evaluation of male streptozotocin-induced diabetic rats, with a reduction in glycosylated hemoglobin levels, increased plasma insulin, hemoglobin and glycogen, i.e., properties that are attributed to the flavonoids present in the drink. A similar effect was found by Dashti et al. (Dashti & Morshedi 2000) when they followed up 15 diabetic rats induced by intraperitoneal injection of Streptozotocin and noted that kombucha may lower blood glucose levels (Alkhatib & Atcheson 2017).

The potential of kombucha to act on glucose regulatory pathways as antihyperglycemic agents in the prevention or treatment of diabetes has been noted, as mentioned earlier in the study by Srihari et al. (Srihari et al. 2013). Black tea and green tea in isolation showed positive effects on glycemic control, but the effects were enhanced with the use of kombucha, as it contains higher antioxidant properties which are attributed to the fermentation process (Bhattacharya et al. 2013). The mechanism that triggers this can perhaps be attributed to the phenolic compounds present in kombucha. including caffeine derivatives, procyanidins and chlorogenic acid, which demonstrate improved insulin sensitivity, vascular endothelial function, nutrient metabolism and the presence of anti-inflammatory mediators (Alkhatib et al. 2017; Johnston et al. 2003; Matsui et al. 2006; Rodríguez-Ramiro et al. 2011). These results suggest that kombucha can effectively be regarded as a potential food in future treatment applications as well as be used for prevention of diabetes (Dashti and Morshedi 2000).

Several mechanisms have been put forward to explain the effects of polyphenols present in kombucha, including catechin and epigallocatechin gallate (ECGC), which have been shown to be highly effective in inhibiting the 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) enzyme in experimental models and linked to metabolic disorders, one of them being DM2 (Alkhatib et al. 2017).

11 $\beta$ -HSD1 is a key enzyme in the metabolism of corticosteroids in peripheral tissues. Increased activity has been implicated in the pathogenesis of central obesity, metabolic syndrome (MS) and the differentiation between glucose and lipid metabolism. Previous animal studies have shown that inhibition of 11 $\beta$ -HSD1 may contribute to the treatment of MS components and obesity-related disorders, which supports the hypothesis that selective inhibition of 11 $\beta$ -HSD1 could be used to treat MS and diabetes (Alkhatib et al. 2017).

Certain bioactive agents present in kombucha, such as thiazolidinediones and fibrates, have an inhibitory effect on 11 $\beta$ -HSD1 (Alkhatib et al. 2017). Given that preliminary results from experimental and human studies have shown positive effects on glucose and lipid metabolism, weight reduction and adipokine levels, further studies are needed to ascertain which therapeutic dose is suitable, and what the maximum tolerated amount is. The bioavailability of these components can be indicated without impairing the broad physiological effects exerted by cortisol, namely carbohydrate regulation, protein and lipid metabolism, regulation of cell growth and development, influence on cognitive function, and mineralocorticoid activity. Since they are involved in MS components and obesity-related disorders when there is overexpression of enzyme 11 $\beta$ -HSD1, the compounds that inhibit 11 $\beta$ -HSD1 are being developed or more precisely, the role of enzyme activity and the bioavailability of its compounds are promising findings that need to be confirmed in placebo-controlled studies with kombucha (Anagnostis et al. 2013).

Many studies have reached the same conclusions about weight loss and insulin deficiency, i.e., it is caused by a hormone that has direct and indirect effects on protein deposition in cells. This hormone increases the intensity of amino acid transport for protein synthesis and, as mentioned earlier, one of the mechanisms of DM pathophysiology when insulin deficiency occurs, is weight reduction, which can be explained by several factors (Bhattacharya et al. 2013). One of the reasons is the increase in inflammation caused by DM, which results in the breakdown and degradation of muscle fibers and adipose tissue (Bhattacharya et al. 2013). The study by Srihari et al. (Srihari et al. 2013) states that insulin hormone anabolism allows glucose to enter tissues and corroborates the hypothesis that insulin deficiency can give rise to cachexia owing to the protein and fat degradation that leads to glycogenesis.

In the absence of insulin, essentially all phases of fat metabolism are accelerated with the release of large amounts of fatty acids into the blood. These fatty acids can be used as a source of energy by muscle cells and most of them are stored in the liver, where they are converted to triglycerides, phospholipids and cholesterol. This rapid hepatic fatty acid metabolism promotes the formation of acetoacetic acid and can lead to severe generalized acidosis, often resulting in acidic coma and even death (Buczowska & Jarosz-Chobot 2001; Dimitriadis et al. 2011).

This effect on unwanted weight loss was found in the study by Morshedi et al. (Morshedi et al. 2006), which evaluated the weight of diabetic rats. There were no significant differences in rat weight before and after the induction of diabetes with the use of kombucha, and the beverage could protect against unwanted weight loss in rats. Similar effects of kombucha on weight in diabetic rats were found in the study by Hosseini et al. (Hosseini et al. 2015), which investigated the fact that a greater degree of protection was provided by kombucha against unwanted weight loss among rats than was the case with the control group. The same authors believe that flavonoids contained in green tea and black tea, the basis of kombucha, may have beneficial effects on weight control in rats owing to their maintenance of glycemic levels and improved insulin sensitivity.

Beneficial results for body weight control were also found in populations that were clinically obese or overweight, as in the study by Tsang et al. (Tsang et al. 2012), in which a link was established with the consumption of phenolic compounds that induce the metabolic regulation of cortisol. The mechanism responsible for this effect has been attributed to the potential ability of phenolic compounds to bind directly to the active site of the 11 $\beta$ -HSD1 receptor (Alkhatib et al. 2017). These findings demonstrate that phenolics can act as new metabolic inhibitors, and have benefits to human health. Moreover, they suggest that there is a link between cortisol, glucose, insulin, blood pressure and the lipid profile that may be of great significance, as

polyphenols influence the metabolic parameters related to DM2 (Alkhatib & Atcheson 2017; Alkhatib et al. 2017; Rodríguez-Ramiro et al. 2011).

There was also an assessment of the effects of kombucha on changes that could lead to an improvement in our quality of life and health, increase body weight and encourage a greater food intake among animals with the aim of enabling them to gain weight, such as broilers (Afsharmanesh & Sadaghi 2014). The desired effect on weight was also found in rats; it served to stabilize or prevent weight loss. In these cases, a positive effect was found in the use of kombucha since body weight control was achieved by means of an anti-obesity factor which had the task of balancing the metabolism that limits fat accumulation (Yang et al. 2011).

Hosseini's study (Hosseini et al. 2016) of 50 diabetic rats found that consumption of kombucha with green tea showed a significant reduction in glycemic levels and lipid levels such as LDL-c, cholesterol, triglycerides and increased HDL-c, when compared with kombucha with black tea.

The results of the meta-analysis were displayed in a forest plot graph, and they showed a standardized mean difference and 95% confidence interval for the studies by Hosseini et al. (Hosseini et al. 2016) and Bhattacharya et al. (Bhattacharya et al. 2013), which showed an effect of kombucha prepared with green tea on the triglyceride profile and lipid profile. They concluded that it had beneficial effects on rats and increased HDL-c, which suggests the need for future evaluative studies with humans.

The beneficial effects of polyphenols (particularly flavonoids) in foods are a promising phenomenon. However, nutritional strategies focused on DM2 modulation and its comorbidities warrant further investigation, with the need for a particular focus on its bioavailability and metabolite bioactivity (Alkhatib & Atcheson 2017; Ernst 2003; Kapp & Sumner 2019).

An important limitation found in this study was the fact that there were few studies that could be included in this SR and meta-analysis, in addition to the high risk of bias, which probably imposed a constraint on the benefits of using kombucha.

Kombucha has been found to have different qualities depending on the brewing method, temperature conditions and fermentation time of the drink and, thus, it shows different compositional profiles (Srihari et al. 2013). Ansari et al. (Ansari et al. 2019), in a recent study, conducted an analysis of the composition of kombucha under storage conditions at temperatures of 20° and 30°C in content of glucuronic acid. They found that there was a variation in glucuronic acid production at temperatures of 20°C. 17 mg / L on Day 1 to approximately 27.2 mg / L on Day 21, with a significant difference ( $p < 0.05$ ) at 30°C, changing from 42.2 mg / L on Day 1 to 48.0 mg / L on Day 21. The amount of glucuronic acid produced in storage conditions at 30°C was significantly higher than at 20°C ( $p < 0.05$ ) (Amarasinghe et al. 2018; Uțoiu et al. 2018).

## 6. Conclusion

Although today the Kombucha drink is widely known throughout the world, its biological properties and health effects are not well understood. The results of this RS and metanalysis demonstrate that the use of kombucha in diabetic rats increases HDL-c levels, but there is no evidence to support the benefits of kombucha on blood glucose and body weight in diabetic rats. Scientific research performed on humans is necessary to understand the mechanism of action through its metabolites to be considered a healthy functional beverage for human consumption, with evidence of the effects of its consumption.

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