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Review Article

Efficacy of *Ilex paraguariensis* versus Placebo on Lipid Profile in Randomized Clinical Trial: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: The use of medicinal plants have been increasing progressively around the world and been associated with decreasing Total Cholesterol (TC) and Low-Density Lipoprotein-Cholesterol (LDL-C) and, increasing High-Density Lipoprotein-Cholesterol (HDL-C) in humans. *Ilex paraguariensis*, known as yerba mate, is rich in bioactive compounds, especially chlorogenic acid has been shown as one of the major contributor to hypocholesterolemic. This review aimed to demonstrate if *Ilex paraguariensis* supplementation is more effective than placebo on lipid profile in randomized placebo-controlled trial. **Methods:** A careful search was performed in PubMed, Web of Science, SciELO, Scopus and Cochrane Library, published until May 2020. The following keywords of Medical Sub Headings (MeSH) were used as search terms: ("yerba mate" OR "*Ilex paraguariensis*") AND ("dyslipidemia" OR "hyperlipidemia") AND ("clinical trial" OR "Randomized Controlled Trial (RCT)" OR "randomly"). **Results:** The literature search identified 149 "*Ilex paraguariensis* x clinical trials", 16 full-text assessed. After, following the inclusion and exclusion criteria, only 3 studies were chosen to qualitative and quantitative synthesis. The study showed that *Ilex paraguariensis* could improve HDL-C, but with no differences in TC and triglycerides, comparing to placebo-controlled group. **Conclusion:** The three included clinical trials have demonstrated high quality, low bias and HDL-C statistically different. To validate the last result, more clinical trials interventions are necessary, Although TC and triglycerides did not demonstrated differences statistically and increasing HDL-C may improve or protect the metabolism of lipid profile, after been supplemented by *Ilex paraguariensis*, compared to placebo-controlled trial.

Key words: *Ilex paraguariensis*, Yerba mate, Cholesterol, Dyslipidemia, Obesity, Randomized placebo-controlled clinical trial.

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INTRODUCTION

It is well established that unbalanced lipid profiles, demonstrated by high Total TC, high LDL-C and low HDL-C concentrations have been the major risk factors of cardiovascular diseases.[1,2] As a preventive or curative strategy, lifestyle modification such as healthy food choices, weight control and physical activity should be mandatory.[1] Therefore, the use of medicinal plants have been increasing progressively around the world and some studies have associated them with decreasing TC and LDL-C and, increasing HDL-C in human and animals studies.[3-5]

Regarding healthy-eating habits, bioactive compounds or chemical components, such as polyphenols, flavonoids, catechins, chlorogenic acid found in fruits, vegetables and also herbal teas could be used daily as an excellent preventive strategy, since the studies have demonstrated their protective effect on human health against chronic diseases, particularly in the cardiovascular system.[6] *Ilex paraguariensis* A.St.Hil., known as yerba mate, from the Aquifoliaceae family, found in the subtropical region of South America.[7] It is a traditional beverage consumed in Brazil, Paraguay, Argentina and Uruguay, which is prepared as a hot infusion of dried and minced leaves, with a bitter taste and pleasant aroma, thus its tea is known as chimarrão, tererê or mate.[8,7] Moreover, this plant is also rich in bioactive compounds, such as caffeoyl derivates (caffeic, dicaffeoylquinic and chlorogenic acid), rutin, kaempferol, quercetin, saponins and xanthines (caffeine, theobromine and theophylline), which the caffeine is responsible for its stimulant properties.[9,10] Besides, chlorogenic acid has been shown as one of the major contributors to hypocholesterolemic among these bioactive compounds.[11]The leaves of yerba mate have been used as a medicinal plant as hypoglycemic, stimulant, hypolipidemic, weighting loss as well oxidative stress protection and cancer, all of them associated with their bioactive compounds.[12-15]

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The present systematic review with meta-analyses aimed to demonstrate if *Ilex paraguariensis,* as a supplement, is more effective than a placebo on lipid profile in randomized placebo-controlled clinical trial (RPCT).

METHODS

The protocol for carrying out this systematic review was developed by following the guidelines of Cochrane Collaboration[16] and described according to PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[17] Since PROSPERO has focused on COVID-19 registrations during the 2020 pandemic, our registration was automatically rejected.

Search strategy

A careful search was performed in PubMed, Web of Science, Lilacs, SciELO, Scopus and Cochrane Library, published until July 2020. The following keywords of Medical Sub Headings (MeSH) were used as search terms: ("yerba mate" OR "*Ilex paraguariensis OR*") AND ("dyslipidemia" OR "hyperlipidemia" OR "Lipid") AND ("clinical trial" OR "RCT" OR "randomly"). Besides, it was included studies obtained by manual search in the reference lists of the articles found initially. Studies were included if they followed all the eligibility criteria presented at the PICOS model.[16]

Inclusion and Exclusion criteria

Inclusion criteria were pre-established using PICOS acronym, like the following:

(P) Participants: Overweight and obese population, any age and gender;

(I) Intervention: Any kind of yerba mate use (tea, extract or capsule);

(C) Control: placebo;

(O) Outcomes: serum levels of triacylglycerol (TG), TC, LDL-C and HDL-C;

(S) Study: Randomized controlled trials.

Only studies published in Spanish, English and Portuguese, with full access were included. Studies evaluating yerba mate associated with physical exercise, supplements, medication or dietary are excluded.

Data extraction

Two researches independently screened the articles. In the first screening, titles and abstracts of the articles were identified. In the second stage, the full-texts of relevant articles were selected based on the eligibility criteria. Divergences were solved with third research by consensus. The detailed information from each study was listed as following: Characteristics (authors 'names, year, country, sample size, supplement, type of the study and trial duration), population characteristics (gender, age, body mass index) and outcomes (dyslipidemia results).

Risk of bias and quality assessment

The risk of bias was assessed using the Cochrane Collaboration´s tool for assessing the Risk of Bias,[16,18] and Jadad scale for reporting randomized controlled trials.[19]

Data analysis

Meta-analysis was carried out using Review Manager (RevMan) 5.3 software provided by the Cochrane Collaboration. Heterogeneity was assessed through I^2 statistics. $I^2 \geq 50\%$ or p represented high heterogeneity. We performed a random effect model because there was a high heterogeneity. Statistical significance was set to $P < 0.05$. To investigate R, SEM and mean, the statistical analysis was using GraphPad Prism Software (Graph Pad Software, Inc. La Jolla, CA, USA, version 7.0), significance was considered at $p < 0.05$.

RESULTS

Summary of included studies

The literature search identified 149 "*Ilex paraguariensis* x clinical trials x lipid", 16 were full-text assessed. After, following the inclusion and exclusion criteria, only three studies were chosen for qualitative and quantitative synthesis (Figure 1).

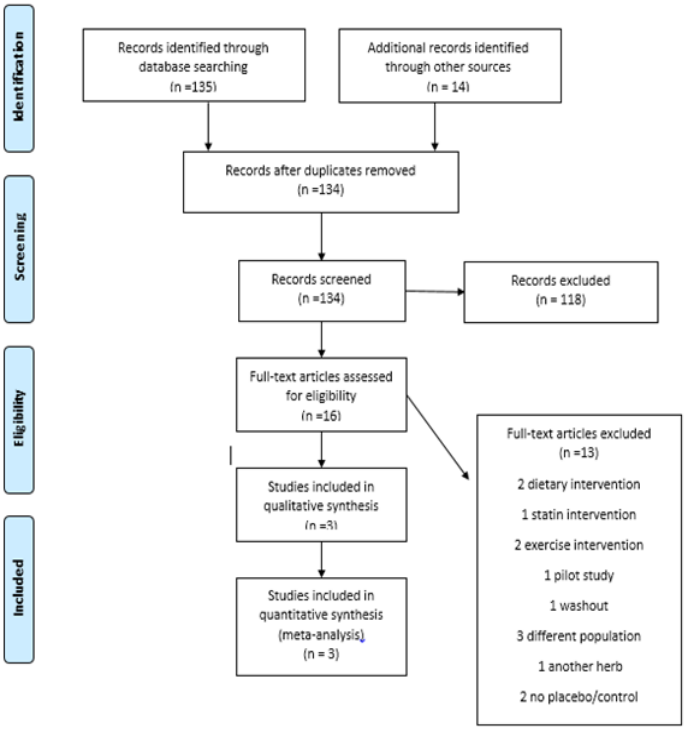

Figure 1: Literary search result in search databases.

Study characteristics

After following the exclusion criteria, we analyzed three clinical trials and basic characteristic was summarized, in Table 1. Population characteristics were demonstrated in Table 2 and the outcomes in Table 3. The Jadad score, for the three chosen trials, was four, which means high quality of the studies. On Table 4, differences between Means, SEM and R from the three studies were introduced in the meta-analysis

Table 1: Characteristics of the included studies.

Author	Country	N	Supplement	Therapy duration (week)	Jadad score
[12]	Korea	60	Mate extract	3 weeks and 6 weeks	4
[20]	Korea	37	Mate capsules	6 weeks and 12 weeks	4
[21]	Korea	60	Mate tablet	6 weeks	4

Table 2: Population characteristics of the included studies and lipid profile before supplementation.

Author	Gender	Age Mate Group (Mean ± SD)	Age Placebo Group (Mean ± SD)	BMI Mate Group (kg/m²) (Mean ± SD)	Diagnostic	TC Mate group (mg/dl) (Mean ± SD)	TG Mate Group (mg/dl) (Mean ± SD)	HDL-C Mate Group (mg/dl) (Mean ± SD)	LDL-C Mate Group (mg/dl) (Mean ± SD)	TC Placebo Group (mg/dl) (Mean ± SD)	TG Placebo Group (mg/dl) (Mean ± SD)	HDL-C Placebo Group (mg/dl) (Mean ± SD)	LDL-C Placebo Group (mg/dl) (Mean ± SD)	N
[12]	Women	28.0 ± 4.8	27.0 ± 5.1	NR	Overweight	182.1 ± 34.0	95.6 ± 46.8	49.0 ± 9.7	NR	182.1 ± 25.5	89.2 ± 33.6	50.1± 10.8	NR	30
[20]	Women/ Men	41.5 ± 11.6	44.9 ± 9.6	28.62 ± 2.09	Obesity	193.6 ± 24.8	141.5 ± 79.9	45.4 ± 7.7	120.9 ± 27.5	176.7 ± 28.8	123.1 ± 65.8	52.3 ± 12.0	101.7± 25.6	15
[21]	Women	45.59 ± 8.93	41.69 ± 11.38	27.58 ± 1.72	Obese	220.00 ± 30.23	NR	NR	NR	199.00 ± 30.23	NR	NR	NR	33

NR (not related), SD= standard definition, BMI= Body Mass Index TC=Total Cholesterol, HDL-C= High Low-Density Lipoprotein-Cholesterol, LDL-C= Low High-Density Lipoprotein-Cholesterol, TG= Triacylglycerol

Table 3: Included studies, outcome information available after *Ilex paraguariensis* (mate) and placebo supplementation.

Author	TC (mate group) (Mean ± SD) (mg/dl)	TG (mate group) (Mean ± SD) (mg/dl)	HDL-C (mate group) (Mean ± SD) (mg/dl)	LDL-C mate group) (Mean ± SD) (mg/dl)	TC (placebo group) (Mean ± SD) (mg/dl)	TG (placebo group) (Mean ± SD) (mg/dl)	HDL-C (placebo group) (Mean ± SD) (mg/dl)	LDL-C (placebo group) (Mean ± SD) (mg/dl)
[12]	172.3 ± 31.6	98.5 ± 44.5	45.1 ± 10.8	NR	183.2 ± 21.2	89.8 ± 32.7	48.5 ± 11.4	NR
[20]	197.9 ± 33.2	130.6 ± 96.3	48.0 ± 10.3	117.8 ± 28.8	172.3 ± 33.9	107.2 ± 53.8	50.4 ± 8.3	97.2 ± 27.5
[21]	208.18 ± 42.58	NR	NR	NR	186.75 ± 25.94	NR	NR	NR

Standard deviation (SD), Total Cholesterol (TC), High Low-Density Lipoprotein-Cholesterol (HDL-C), Low High-Density Lipoprotein-Cholesterol (LDL-C), Triacylglycerol (TG)

Table 4: Differences between Means, SEM and R from the three chosen studies to be introduced in the meta-analysis.

	N	MATE TC	R TG	R LDL-C	R HDL-C	Placebo TC	R TG	R LDL-C	R HDL-C
[12]	30/22	-9.8 ± 9.267 R 0.02188	2.9 ±12.87 R 0.00101	NR	-3.9 ±2.856 R 0.0359	1.1 ±6.677 R 0.00054	0.6 ±9.326 R 8.278	NR	-1.6 ±3.103 R 0.5288
[20]	15	4.3 ± 10.7 R 0.0057	-10.9 ± 32.31 R 0.00404	-3.1 ±10.28 R 0.0032	2.6 ±3.32 R 0.0214	-4.4 ±11.49 R 0.0052	-15.9 ±21.95 R 0.0184	-4.5 ±9.701 R 0.0076	1.9 ±3.767 R 0.00900
[21]		11.82 ± 13.29 R 0.02039				- 12.25± 9.724 R 0.04536			

Means, SEM (Standard Error of Mean) and R (correlation coefficient)

Risk of bias

All studies presented a low risk of bias for five domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and selective reporting). The risk of bias was unclear for two domains of all studies (incomplete outcome data and other bias). The graph presented as percentages in Figure 2 and the risk of bias assessment in Figure 3.

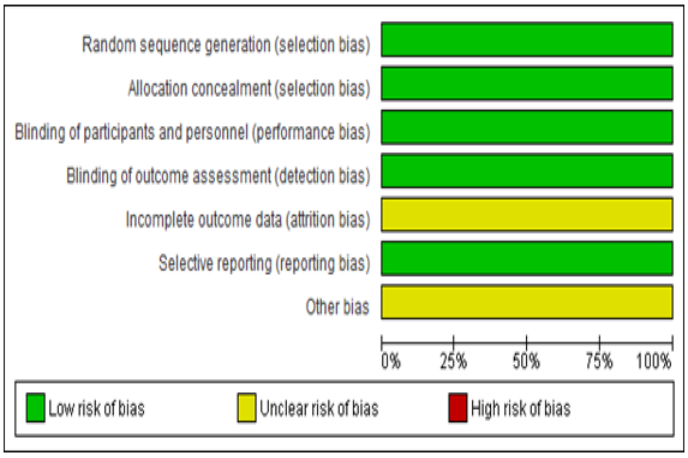

Figure 2: Risk of bias graph presented as percentages across the three included studies.

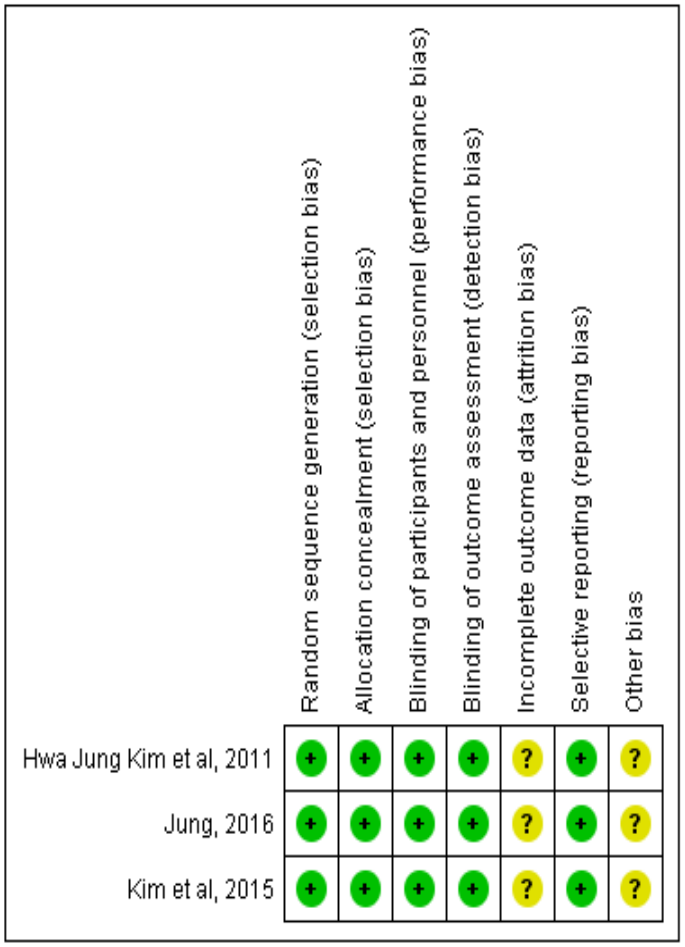

Figure 3: Risk of bias assessment in included studies.

Meta-analysis

Figure 4 represents the forest plots resulting from the meta-analysis for the considered outcomes. The first analysis A when TC was analyzed, the result demonstrated 64% of heterogeneity and[12] was responsible for the high heterogeneity of this study. Therefore, the random process was used and analyzed, the data demonstrated that was not significant between placebo and *Ilex paraguariensis* groups. The second analysis (B) was triacylglycerol analyzed, it is possible to see, that *Ilex paraguariensis* supplement compared to placebo, was not significantly different. Finally, the third analysis (C) was with HDL-C between placebo x *Ilex paraguariensis*, only two studies among the three were compared and the result showed significant increasing of HDL-C with low heterogeneity (3%), in this case, more participants and studies would demonstrate the robustness of results and conclusion in this research.

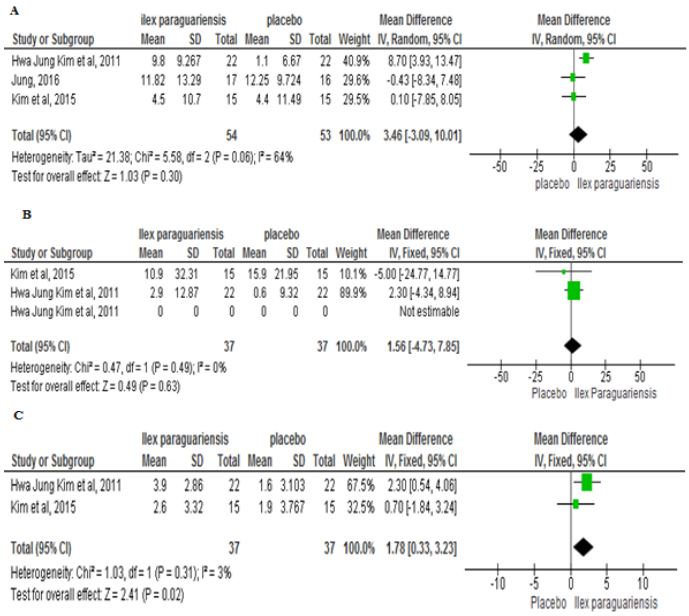

Figure 4: Forest plot of the meta-analysis for the scores of lipid profile. (A) Mean differences in TC, between *Ilex paraguariensis* and placebo. (B) Mean differences in triacylglycerol, between *Ilex paraguariensis* and placebo. (C) Mean differences in HDL-C, between *Ilex paraguariensis* and placebo.

DISCUSSION

The use of medicinal plants has been traditionally used in folk medicine and is increasing in many parts of the world, as part of the popularity of complementary and alternative medicine.[3,22] Besides, plants with medicinal properties are frequently considered less toxic and freer form side effects than synthetic medicines.[23] However, there are few published RCT to evaluate their efficacy and safety,

Lipid profile has been involved in high concentration of TC, which increases the risks of cardiovascular diseases, low plasma TG and LDL-C levels, which are associated with lower cardiovascular risk.[24] Moreover, low HDL-C is part of metabolic alterations such as the accumulation of dense and small LDL-C, high level of triglycerides and insulin resistance. All of them together can cause an effect on cardiovascular diseases and complications in type 2 diabetes.[11] HDL-C can antagonize the effects of LDL-C oxidation on endothelial. and smooth muscle vascular cells and reverse cholesterol transport.[25]

One of the risk factors for atherosclerosis is when the serum level of HDL-C is reduced. Low HDL-C is often part of a set of metabolic

alterations including hypertriglyceridemia, accumulation of small and dense LDL-C levels and insulin resistance. HDL effect is mostly attributed to its central function in the reverse cholesterol transport, a process whereby excess cell cholesterol is taken up and processed by HDL particles for further delivery, for metabolism, to the liver and bile excretion.[25] According to (Libby, 2000), a high concentration of TC increases the risks of cardiovascular diseases and low plasma TG and LDL-C levels are associated with low risks,[5]

Ilex paraguariensis extracts are especially rich in chlorogenic acid, which may demonstrate effects in hyperlipidemia. Chlorogenic acid is a bioactive compound found ubiquitously in plants. Moreover, this acid is formed by quinic acids and caffeic acid, which is involved in glucose metabolism and to reduce cardiovascular disease by decreasing, triacylglycerol, TC and LDL-C. Thus, chlorogenic acid contains hypoglycemic and hypocholesterolemic effects.[26,11]

Although there are differences between animals and humans in lipid metabolism, there is evidence from pre-clinical studies *in vitro* and *in vivo* demonstrating the beneficial effects of *Ilex paraguariensis* in dyslipidemia decreasing levels of LDL-C, TC and triglycerides and increasing HDL-C.[27-30]

The present study is the first systematic review with a meta-analysis that analyzed the lipid profile in people supplemented by yerba mate. Results showed that *Ilex paraguariensis* could improve HDL-C, but with no differences in TC and triglycerides, comparing to the placebo-controlled group. Unfortunately, LDL-C could not be analyzed statistically because only one study showed the result.

This study demonstrated some limitations; the small number of individuals for each clinical trial and unfortunately only a few clinical trials have been associated *with Ilex paraguariensis* and cholesterol, up to the present.

Although, triglycerides and HDL-C the data showed a beneficial effect on HDL-C levels after individuals being supplemented by yerba mate comparing to a placebo-controlled group,

Further evidence is necessary to clarify if this plant can protect or decrease lipid profile to reduce the risks of cardiovascular diseases.

CONCLUSION

Although TC and triglycerides did not demonstrate differences statistically, increasing HDL-C may improve or protect the metabolism of lipid profile, after been supplemented by *Ilex paraguariensis* compared to placebo-controlled trial.

RCTs are necessary, especially due to the small number of studies and participants

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CONFLICT OF INTEREST

All authors of the present study declare; they have no conflicts of interest.

ABBREVIATIONS

BMI: Body Mass Index; **R:** Correlation coefficient; **HDL-C:** High Low-Density Lipoprotein-Cholesterol; **LDL-C:** Low High-Density Lipoprotein-Cholesterol; **MeSH:** Medical Sub Headings; **NR:** Not related; **RCT:** Randomized Controlled Trial; **RPCT:** Randomized placebo-controlled clinical trial; **RevMan:** Review Manager; **SD:** Standard definition; **SEM:** Standard Error of Mean; **TC:** Total Cholesterol; **TG:** Triacylglycerol.

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