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SYSTEMATIC REVIEW

Cinnamon extract effects on insulin resistance, metabolic factors, and menstrual cyclicity of women with polycystic ovary syndrome: A systematic review and meta-analysis [version 1; peer review: awaiting peer review]

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Abstract

Background: Cinnamon is a herbal medicine that is supposed to improve the metabolic disorder polycystic ovary syndrome (PCOS), but there is still no data about the effectiveness and efficacy of this herbal medicine for the metabolic parameters of PCOS. This study aims to systematically evaluate the effects of cinnamon extract on improving insulin resistance, lipid profile and regularity of menstruation in PCOS women.

Methods: This is a systematic review and meta-analysis of randomized controlled trials (RCTs) studies. We searched the MEDLINE, Cochrane, Google Scholar, and PubMed databases to identify relevant studies using cinnamon extract effects on insulin resistance, metabolic factors, and menstrual cyclicity of PCOS women.

Results: Five RCTs consisting of 206 women were included in the meta-analysis. Significant differences were found in fasting blood glucose (FBG) (mean difference (MD)= -4.8 mg/dL, 95% CI: -8.04 to -1.57, p=0.004; 143 participants), High-Density Lipoprotein (HDL-cholesterol, HDL-C) (MD= -27.24 mg/dL, 95% CI: -32.62 to -21.85, p< 0.00001; 143 participants, Insulin level (MD = -2.20 mIU/dL, 95% CI: -4.17 to -0.23, p=0.03; 143 participants), and menstrual cyclicity in six months (MD= 2.28, 95% CI: 1.83 to 2.73, p< 0.00001; 33 participants) were obtained.

Conclusion: Cinnamon can be a potential supplementary therapy agent for PCOS women as it improves fasting blood glucose, insulin level, HDL–cholesterol and menstrual cyclicity in PCOS women.

Keywords

Cinnamon, insulin resistance, metabolic factors, menstrual cyclicity, polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common and complex endocrine dysfunctions affecting 5-10% of fertile women.[1] Manifestations of PCOS include hyperandrogenism (hirsutism, acne, obesity), reproductive dysfunction (infertility, menstrual irregularity, miscarriage, pregnancy complications), and metabolic complications (dyslipidemia, insulin resistance).[2,3] PCOS is a combination of a reproductive and metabolic condition with psychological consequences. Patients suffer from anxiety, depression and distress due to its clinical manifestation.

Insulin resistance, dyslipidemia, and diabetes are some hyperandrogenic manifestations of PCOS.[4] Insulin resistance presents in 60-80% of PCOS women, as well as 95% in overweight women.[5,6] Insulin resistance has a major role in the development of cardiovascular and metabolic disturbances. Cells fail to respond to insulin thus excess glucose is not completely absorbed by cells and increases the level of blood sugar.[4] Dyslipidemia is one of the metabolic consequences of PCOS. The prevalence of dyslipidemia is three times more likely in patients with PCOS than in normal women.[7] The other manifestation of hyperinsulinemia is irregular menstrual cyclicity because of the disruption of folliculogenesis and abnormal androgen secretion.[6]

There are some therapies for PCOS. Nonpharmacologic therapy consists of physical activities for weight reduction and managing diet intake. Two pharmacological drugs used for treating insulin resistance of PCOS are metformin and thiazolidines. But the gastrointestinal effects (61.5% suffer from nausea and vomiting, 59.1% abdominal pain as well as cramping and 64.9% diarrhoea) of these drugs make patients feel uncomfortable.[5,8] Thus, alternative herbal medicine is a good choice with less adverse effects.

Cinnamon (*Cinnamomum zeylanicum)* is a natural medicine recently used as a complementary medicine for decreasing hyperglycemia, dyslipidemia, and other metabolic disorders of PCOS.[5,8] A procyanidin substance from cinnamon extract stimulates autophosphorylation of the insulin receptor and inhibits protein tyrosine phosphate thus increasing insulin-stimulated glucose uptake and glycogen synthesis. It also reduces fasting glucose, triglycerides, low-density lipoprotein (LDL) and total cholesterols.[5,8] Some studies prove that cinnamon can reduce hemostatic model assessment for insulin resistance (HOMA-IR) in PCOS patients.[4,5] It also improves menstrual cyclicity in PCOS patients. However, no studies have evaluated the effectiveness of these extracts on insulin resistance, lipid profile, and regularity of menstruation in PCOS women. Thus, this study was conducted to systematically evaluate the effects of cinnamon extract on improving insulin resistance, lipid profile and regularity of menstruation in PCOS women.

Methods

Study selection criteria and search strategy

The search strategy was carried out by two independent authors (R.W., A.A.) separately from January 2019 to November 2020. To be included the study design had to be a randomized controlled trial in humans.

A systematic review of published articles was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; identification number CRD42021214007 on 21/01/2021).

The first step, a bibliographic search was performed on MEDLINE, Cochrane, Google Scholar, PubMed database using search terms; (((((((("Polycystic ovarian syndrome" OR "PCOS") AND ("Cinnamon" OR "*Cinnamomum zeylanicum*") AND ("Insulin resistance" OR "HOMA IR") AND ("Body mass index" OR "BMI") AND ("Trygliceride") AND ("Cholesterol") AND ("Insulin level" OR "Blood insulin") AND ("Menstrual cyclicity OR "Regularity of menstruation")))))))), from January 2019 to September 2020. In order to eliminate bias, we do not limit the language. Literature reviews, book chapters, animal experimental articles were excluded. The related articles were then screened one by one manually in order to select the appropriate topics.

Secondly, we screened all duplicated articles based on the title and abstracts. Then, the third step was to assess the full text articles for eligibility. Only studies focusing on the effect of cinnamon based on parameter lipid profile, insulin resistance and regularity of menstruation were included in this meta-analysis. We used the PICOS format to examine the study eligibility criteria (Participants, Intervention, Comparison, Outcomes, Study Design) (Table 1). The final step was to combine all selected articles in the meta-analysis.

Data synthesis and quality control of selected studies

Two authors (R.W., A.A.) independently assessed the quality of included studies using the Cochrane 'Risk of Bias Assessment Tool' involving the random sequence generation (selection bias), allocation concealment (selection bias), masking of participants and personnel (performance bias), masking of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Risk of bias is evaluated as low, high, or unclear.

Table 1. Study and patient characteristics of meta-analysis.

Author	Participants	Study design	Sample size	Intervention	Comparison	Outcome
Kort D.H., 2014[10]	PCOS patients aged 18-38 years	Prospective, placebo controlled, double-blinded randomized trial	Cinnamon group: 11 participants Placebo group: six participants	Purified aqueous abstract of cinnamon in 125 mg capsules, which would be taken orally before each meal for six months	Placebo capsules containing ground cereal	Number of menses during the six months study period, change in insulin resistance, change in glucose response
Borzoei A., et al, 2018[11]	PCOS patients aged 20-38 years with a BMI 25-40 kg/m²	Doubled-blind, randomized, controlled trial	Cinnamon group: 42 participants Placebo group: 42 participants	Cinnamon capsule contains 500 mg cinnamon powder administered 1500 mg daily for eight weeks	Placebo capsule (wheat flour) administered three capsules daily for eight weeks	Changes of serum biomarkers (glucose, insulin, HOMA-IR, adiponectin, triglyceride, total cholesterol, LDL Cholesterol, HDL Cholesterol
Hajimonfarednejad M., et al, 2017	Patients aged 18-45 years meeting Rotterdam Criteria for PCOS, BMI equal or greater than 18 kg/m²	Two-arm, blinded, randomized, placebo-controlled clinical trial	Cinnamon group: 29 participants Placebo group: 30 participants	500-mg cinnamon capsules administered three times per day for 12 weeks with a standard treatment regimen (10 mg medroxyprogesterone tablet, from the 15th day of menstruation cycle for 10 days)	Placebo capsule administered three times daily for 12 weeks	Changes in anthropometric factors (weight, BMI, and waist circumference), blood glucose, lipid profile, serum androgen levels, level of fasting insulin, HOMA-IR, LDL and HDL Cholesterol
Wang J.G., et al, 2007	PCOS women, the exclusion criteria approved were: diabetes mellitus, hyperprolactinemia, thyroid disorders, hypertension, and without history of oral hypoglycemic, insulin-sensitizing drugs, oral contraceptive agents, and also β-blockers	Randomized controlled trial, pilot study	Cinnamon group: seven participants Placebo group: seven participants	333-mg cinnamon extract administered three times per day for eight weeks	Placebo capsule administered three times a day for eight weeks	Changes in Body Mass Index, HOMA-IR, fasting and two-hour oral glucose tolerance test
Kort D.H., et al, 2013	Patients 18-38 years old with PCOS	Randomized controlled double-blinded clinical trial	Cinnamon group: 11 participants Placebo group: five participants	Cinnamon supplements were administered 1500 mg/day	Placebo was administered three times a day	Changes in menstrual cyclicity in 6 months

To perform the meta-analysis, Review Manager (RevMan version 5.3, The Cochrane Collaboration, Oxford, UK) was used. The statistical heterogeneity across trials were assessed by I^2 statistic, which describes the percentage of variation, and a value of I^2 greater than 50% was considered heterogeneous. All results were presented as a random-effect model when the detected heterogeneity was significant. The results of this study are displayed by forest plot diagrams.

Results

Flow chart of study selection

Figure 1 shows details of the study selection. The primary search identified 103 articles. We screened title and abstract and found five eligible studies with a full text format. All five articles were included in this review. The five articles were RCTs comparing cinnamon extract and a placebo in PCOS women based on changes in insulin resistance, lipid profile and changes in regularity in menstruation (Table 1). Only two RCTs analyzed showed changes in regularity of menstruation.[9,10]

Characteristics of included studies

The characteristics of included studies are described in Table 1. Two studies focused on Iranian women,[5,11] two others on Caucasian women from Columbia[9,10] and the last focused on New York, USA.[6] Of the five studies, one study was conducted as a pilot study. Diagnosis criteria of PCOS was based on the Rotterdam criteria for all studies, including: hyperandrogenism (elevated serum T level ≥ 80 ng/dL, intermittent or absence of menstrual cycles (ovarian dysfunction), and/or a polycystic ovary in ultrasound with the exclusion of adrenal, ovary, and pituitary disorder.[5]

All studies used the same exclusion criteria for PCOS women who participated in the research. These were diabetes mellitus, hyperprolactinemia, thyroid disorders, liver or kidney disease, Cushing syndrome, cardiovascular disease, seizure, cerebrovascular disorder, hypertension, smoking, current treatment of infertility, allergy to cinnamon, and the use of oral hypoglycemic, insulin-sensitizing drugs, oral contraceptive drugs, and β-blocker in the two to three months prior to the study enrolment.

There were no specific criteria for body mass index as inclusion criteria in the study. Only three studies made a specific range of body mass index (BMI) criteria for enrolling the patient in the study.[5,10,11] The range of BMI was 25-40 kg/m^2, 20-50 kg/m^2 and > 18 kg/m^2.
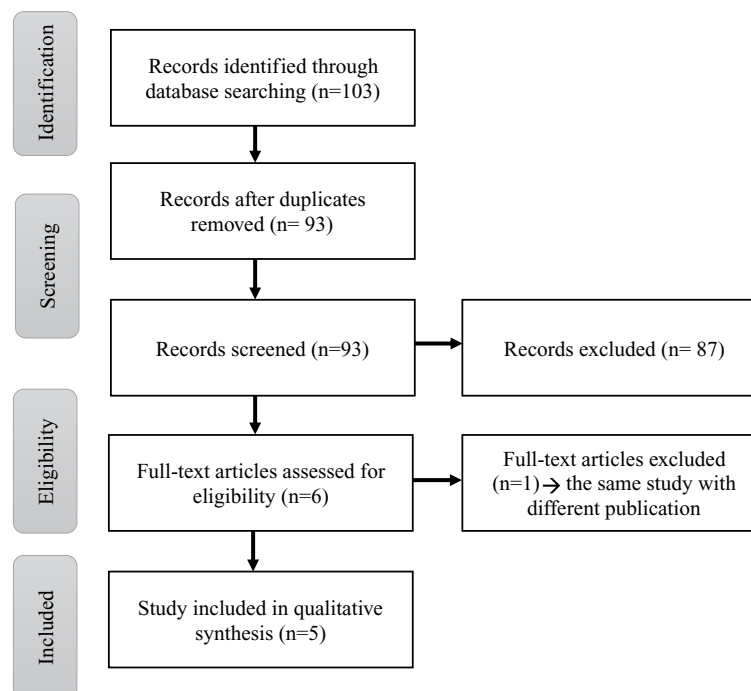

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

The mean age for each group was reported in each study, but not for one study[9] (mean age for all groups was 31.1 ± 2 years old). The mean age in each group reported by Hajimonfarednejad et al.,[5] was not significantly different. The mean age for the cinnamon group and the placebo group in Hajimonfarednejad et al. and Kort and Borzoei et al. was respectively 28.62 ± 5.74 vs 26.53 ± 6.53 years old (p = 0.19); 26.95 (18-34) vs 27.86 (18-38) years old (p = no data); and 29.26 ± 6.14 vs 30.17 ± 6.69 years old (p = no data).[5,10,11]

The dose of cinnamon given for intervention in four studies was the same (1500 mg cinnamon daily). One pilot study, Wang et al., administered 1000 mg cinnamon daily.[6] The length of the observational studies ranged from eight to 24 weeks.

The risk of bias in randomized trials included in the meta-analysis is shown in Figures 2 and 3.
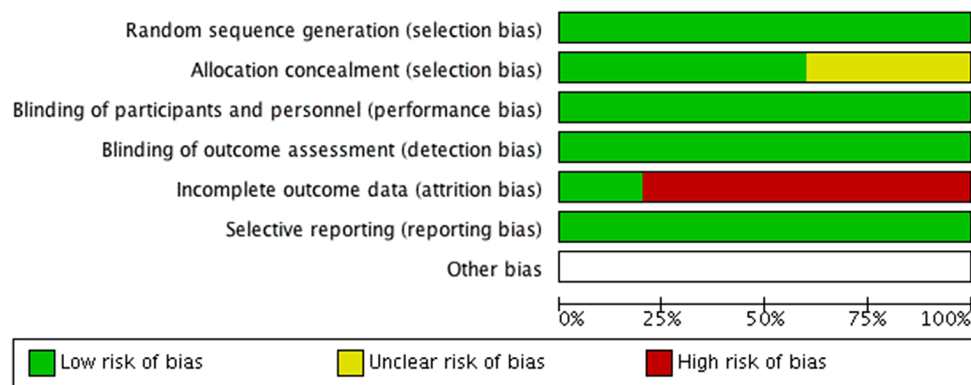
Figure 2. Review of cumulative risk of bias included studies.
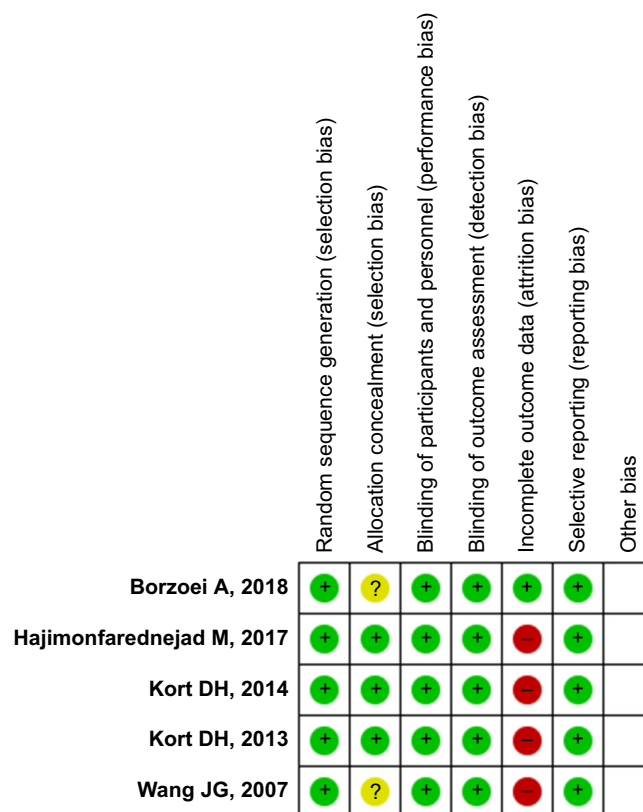
Figure 3. Review of risk of bias in each study.

Qualitative data synthesis and meta-analysis

Weight/body mass index (BMI)

Hajimonfarednejad et al.[5] and Borzoei et al.[11] studied the changes in BMI and weight between the cinnamon and control groups. Hajimonfarednejad et al. found no significant difference in BMI changes in the control group (p = 0.168) and cinnamon group (p = 0.054).[5] But there was a significant difference in weight changes in the control group (p = 0.023) than in the cinnamon group (p = 0.058).[5] Borzoei et al. analysed BMI changes in the cinnamon group (p = 0.002) and found it was significantly different to the control group (p = 0.89).[11] This result was the same with weight changes in the cinnamon group (p = 0.00) compared to the control group (p = 0.85), which showed no significant result.

We found there was no significant mean difference in BMI and weight after intervention with cinnamon as well as the placebo group, respectively (−0.21[−1.80,1.38]; p = 0.79 and 1.08[−2.79,4.96]; p = 0.58) (Figures 4A and 4B).

Insulin resistance (HOMA-IR)

Of the five studies, four studies compared insulin resistance after cinnamon intervention by homeostasis model assessment insulin resistance (HOMA-IR) methods. But only three studies showed significant results in changes of insulin resistance after intervention. There were significant changes in HOMA-IR after cinnamon intervention in the Borzoei et al. study (p = 0.00), Wang et al. study (p ≤ 0.03), and Hajimonfarednejad et al. study (p = 0.001).[5,6,11] Kort found no significant difference in the changes of insulin resistance.[10]

In this meta-analysis, we analyze mean difference of insulin resistance post cinnamon intervention. The result showed no significant difference between insulin resistance post cinnamon and post placebo intervention (−0.19 [−0.54, 0.15], p = 0.27) (Figure 4C).

Fasting blood sugar level

Data from three studies were available for fasting blood sugar level, but Wang et al. did not show complete data thus we could not analyze the results in this meta-analysis. Borzoei et al. found there was a significant difference of fasting blood sugar changes in the cinnamon group (p = 0.00) than in the control group (p = 0.15).[11] But Hajimonfarednejad et al. found no significant difference of fasting blood sugar changes in the cinnamon and control groups (respectively, p = 0.63; p = 0.148).[5]

In this meta-analysis we analyze the mean difference of post intervention fasting blood sugar level between the cinnamon and control groups. There was a significant difference between fasting blood sugar level post intervention in the cinnamon group and control group (−4.8[−8.04, −1.57]; p = 0.004) (Figure 4D).

Lipid profile

Triglyceride level

Data from two studies were available for triglyceride level. Borzoei et al. defined that there was a significant difference in triglyceride changes in the cinnamon group (p = 0.001) than in the control group (p = 0.29).[11] But Hajimonfarednejad et al. found no significant difference in triglyceride changes in the cinnamon and control groups (respectively, p = 0.105; p = 0.935).[5]

In this meta-analysis, we analyze the mean difference of post intervention triglyceride level between the cinnamon and control groups. There was no significant difference between triglyceride level post intervention in the cinnamon group and control group (−10.73[−26.35, 4.88]; p = 0.18) (Figure 4E).

LDL-cholesterol level

Data from two studies were available for LDL-cholesterol level. Borzoei et al. defined that there was a significant difference in LDL-cholesterol changes in the cinnamon group (p = 0.001) than in the control group (p = 0.85).[11] Hajimonfarednejad et al. found the same results as Borzoei et al., they showed a significant difference in LDL-cholesterol changes in cinnamon than in control group (respectively, p = 0.004; p = 0.212).[5,11]

In this meta-analysis, we analyze the mean difference of post intervention LDL-cholesterol level between the cinnamon and control groups. There was no significant difference between LDL-cholesterol level post intervention in the cinnamon group and control group (−3.39[−12.27, 5.50]; p = 0.46) (Figure 4F).

HDL-cholesterol level

Data from two studies were available for HDL-cholesterol level. Hajimonfarednejad et al. defined that there was no significant difference in HDL-cholesterol changes in the cinnamon group (p = 0.238) but there was a significant

A

Study or Subgroup	Cinnamon extract			Placebo				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Borzoei A 2018	30.6	4.99	42	31.6	4.87	42	56.9%	-1.00 [-3.11, 1.11]	
Hajimonfarednejad M 2017	27.44	4.32	29	26.61	5.16	30	43.1%	0.83 [-1.60, 3.26]	
Total (95% CI)			71			72	100.0%	-0.21 [-1.80, 1.38]	

Heterogeneity: Chi² = 1.25, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 0.26 (P = 0.79)

B

Study or Subgroup	Cinnamon extract			Placebo				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Borzoei A 2018	76.1	12.2	42	77.7	12.9	42	52.0%	-1.60 [-6.97, 3.77]	
Hajimonfarednejad M 2017	67.79	9.72	29	63.8	12.08	30	48.0%	3.99 [-1.60, 9.58]	
Total (95% CI)			71			72	100.0%	1.08 [-2.79, 4.96]	

Heterogeneity: Chi² = 2.00, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.55 (P = 0.58)

C

Study or Subgroup	Cinnamon			Placebo				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Borzoei A 2018	3.15	1.59	42	3.92	1.8	42	23.0%	-0.77 [-1.50, -0.04]	
Hajimonfarednejad M 2017	0.61	0.82	29	1.34	1.31	30	39.3%	-0.73 [-1.29, -0.17]	
Kort DH 2014	2.5	0.97	11	1.2	0.78	6	16.9%	1.30 [0.45, 2.15]	
Wang JG 2007	2.57	1.43	15	2.33	0.48	15	20.8%	0.24 [-0.52, 1.00]	
Total (95% CI)			97			93	100.0%	-0.19 [-0.54, 0.15]	

Heterogeneity: Chi² = 19.17, df = 3 (P = 0.0003); I² = 84%
Test for overall effect: Z = 1.09 (P = 0.27)

D

Study or Subgroup	Cinnamon extract			Placebo				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Borzoei A 2018	84.3	10.9	42	99.6	19.8	42	22.4%	-15.30 [-22.14, -8.46]	
Hajimonfarednejad M 2017	85.55	6.52	29	87.33	7.82	30	77.6%	-1.78 [-5.45, 1.89]	
Total (95% CI)			71			72	100.0%	-4.80 [-8.04, -1.57]	

Heterogeneity: Chi² = 11.67, df = 1 (P = 0.0006); I² = 91%
Test for overall effect: Z = 2.91 (P = 0.004)

E

Study or Subgroup	Cinnamon Extract			Placebo				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Borzoei A 2018	96.1	51.4	42	124	55.6	42	46.5%	-27.90 [-50.80, -5.00]	
Hajimonfarednejad M 2017	86.82	44.36	29	82.63	39.04	30	53.5%	4.19 [-17.16, 25.54]	
Total (95% CI)			71			72	100.0%	-10.73 [-26.35, 4.88]	

Heterogeneity: Chi² = 4.04, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 1.35 (P = 0.18)

F

Study or Subgroup	Cinnamon Extract			Placebo				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Borzoei A 2018	105	21.8	42	108	29.6	42	63.9%	-3.00 [-14.12, 8.12]	
Hajimonfarednejad M 2017	90.23	27.24	29	94.3	30.69	30	36.1%	-4.07 [-18.87, 10.73]	
Total (95% CI)			71			72	100.0%	-3.39 [-12.27, 5.50]	

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.46)

Figure 4. A. Forest plot showing the impact of cinnamon extract on body mass index (BMI). B. Forest plot showing the impact of cinnamon extract on weight. C. Forest plot showing the impact of cinnamon extract on insulin resistance (HOMA-IR). D. Forest plot showing the impact of cinnamon extract on fasting blood sugar level* E. Forest plot showing the impact of cinnamon extract on trygliceride level. F. Forest plot showing the impact of cinnamon extract on LDL-cholesterol level. G. Forest plot showing the impact of cinnamon extract on HDL-cholesterol level*. H. Forest plot showing the impact of cinnamon extract on total cholesterol level. I. Forest plot showing the impact of cinnamon extract on insulin level*. J. Forest plot showing the impact of cinnamon extract on DHEA level. K. Forest plot showing the impact of cinnamon extract on menstrual cyclicity in 6 months*.

G

H

I

J

K

Figure 4. (continued)

difference in the control group (p = 0.007).[5] Borzoei *et al.* found the opposite result to Hajimonfarednejad *et al.* and showed a significant difference in HDL-cholesterol changes in the cinnamon group than in the control group (respectively, p = 0.0001; p = 0.06).[11]
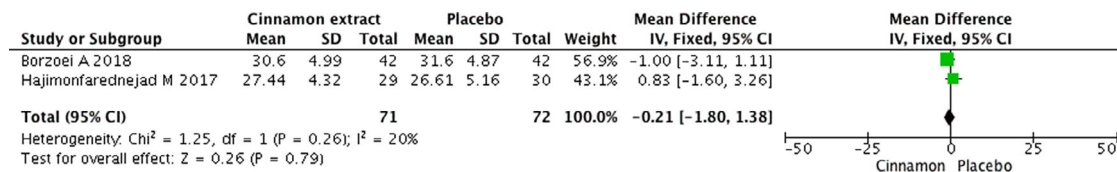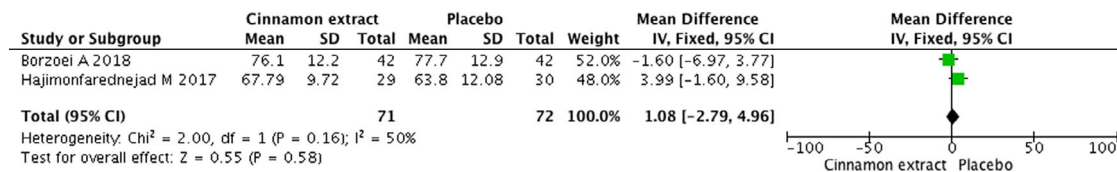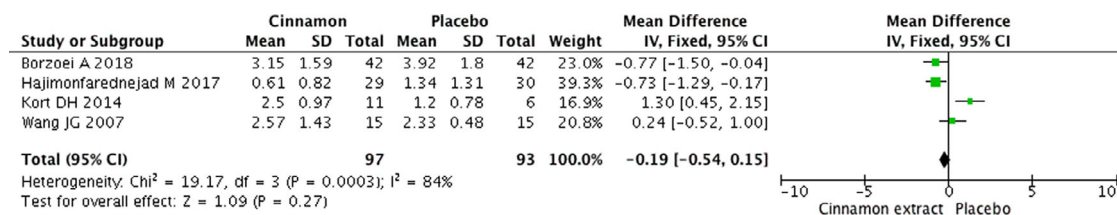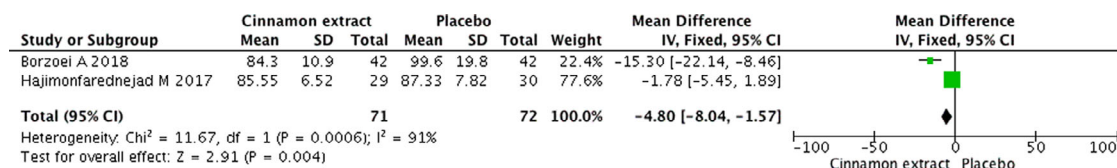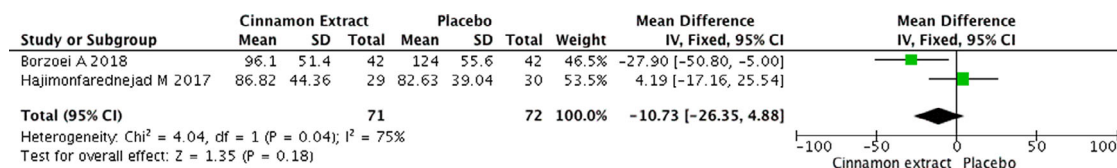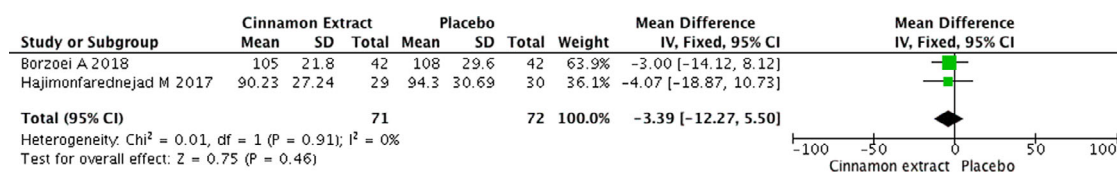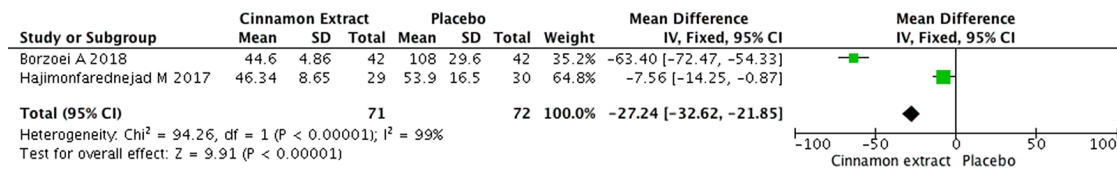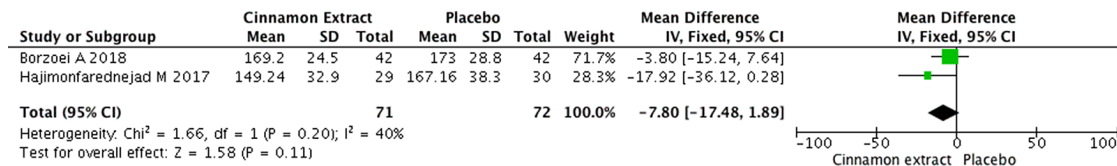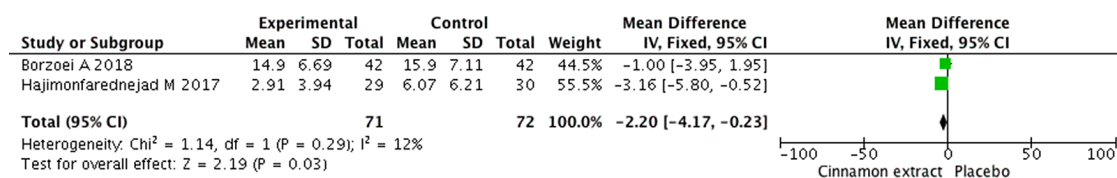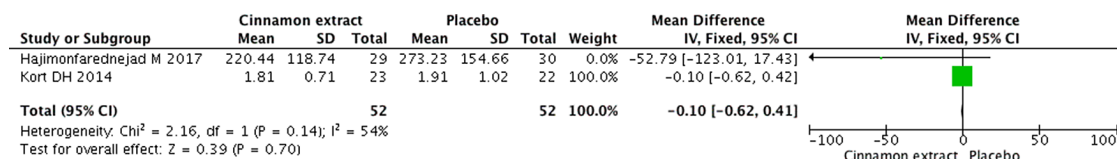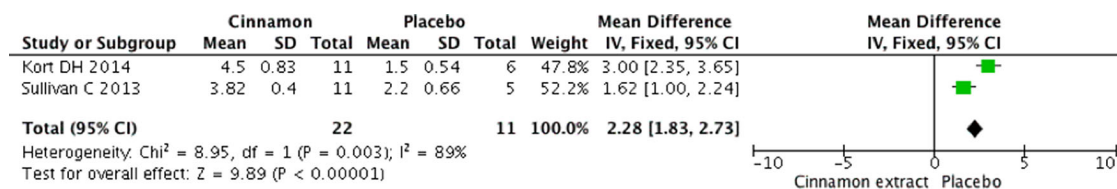
In this meta-analysis we analyze the mean difference of post intervention HDL-cholesterol level between the cinnamon and control groups. There was a significant difference between LDL-cholesterol level post intervention in the cinnamon group and control group (−27.24[−14.25, −0.87]; p < 0.00001) (Figure 4G).

Total cholesterol level

Data from two studies were available for total cholesterol level. Borzoei *et al.* defined that there was a significant difference in total cholesterol changes in the cinnamon group (p = 0.001) than in the control group (p = 0.3).[11] Hajimonfarednejad *et al.* found the same results as Borzoei *et al.*, they showed a significant difference in total cholesterol changes in the cinnamon than in the control group (respectively, p = 0.001; p = 0.685).[5]

In this meta-analysis we analyse mean difference of post intervention total cholesterol level between the cinnamon and control groups. There was no significant difference between total cholesterol level post intervention in the cinnamon group and control group (−7.8[−17.48, 1.89]; p = 0.11) (Figure 4H).

Insulin level

Data from two studies were available for insulin level. Borzoei *et al.* defined that there was a significant difference in insulin level changes in the cinnamon group (p = 0.01) than in the control group (p = 0.19).[11] Hajimonfarednejad *et al.* found that there was a significant difference in insulin level changes in the cinnamon and control groups (respectively, p = 0.001; p = 0.002).[5]

In this meta-analysis, we analyze mean difference of post intervention insulin level between the cinnamon and control groups. There was a significant difference between insulin level post intervention in the cinnamon group and control group (−4.17[−4.17, −0.23]; p = 0.03) (Figure 4I).

Dehydroepiandrosterone (DHEA)

Data from two studies were available for dehydroepiandrosterone (DHEA) level. Hajimonfarednejad *et al.* defined that there was no significant difference in DHEA changes in the cinnamon group and control group (respectively, p = 0.751; p = 0.237).[5] Kort found the same results as Hajimonfarednejad *et al.* and showed no significant difference in DHEA changes in cinnamon than in the control group (p = no data).[10]

In this meta-analysis, we analyze mean difference of post intervention DHEA level between the cinnamon and control groups. There was no significant difference between DHEA level post intervention in the cinnamon group and control group (-0.10[-0.62, 0.41]; p = 0.70) (Figure 4J).

Menstrual cyclicity

Two preliminary studies examined the effect of cinnamon in menstrual cyclicity. Kort *et al.* showed that cinnamon can be a useful adjunct in the treatment of menstrual dysfunction in PCOS women. They showed significant changes in the menstruation cycle after intervention for 24 weeks (p = 0.0076).[10] The results were the same in the Kort *et al.* study, who concluded that there were significant changes in menstrual cyclicity after 24 weeks (p = 0.047).[9]

In this meta-analysis, we analyze mean difference of post intervention menstrual cyclicity between the cinnamon and control groups. There was a significant difference between menstrual cyclicity post intervention in the cinnamon group and control group (2.28[1.83, 2.73]; p < 0.00001) (Figure 4K).

Discussion

This is the first systematic review and meta-analysis to evaluate the effect of cinnamon extract on insulin resistance, lipid profile, and menstrual regularity in PCOS women. We also assess change of BMI, weight and DHEA level as a secondary outcome. This review evaluated the included studies using recommended methodology (PRISMA guidelines). We only analyzed randomized controlled trial studies, which are the most reliable method to test new treatment. Our meta-analysis including five RCTs and within these 190 PCOS women showed an insulin resistance change after cinnamon treatment, and 143 PCOS women showed the lipid profile change, BMI, weight, and menstrual cyclicity changes after cinnamon treatment.

Cinnamon has been used in traditional herb and food industry. The component of cinnamon was extracted from the bark of *Cinnamoni cassia*. Nowadays, cinnamon has been reported to improve insulin sensitivity and increase glucose uptake in 3T3-L1 adipocyte, thus it improves lipid profile.[14]

Obesity changes the phenotypic expression of PCOS, exacerbating metabolic, reproductive, and psychological features. Obesity itself effects ovulatory function, regularity of menstruation, and also infertility status. Thus, prevention of weight gain is recommended for controlling PCOS.[15] The last guideline regarding obesity suggested an initial weight loss of 5-10% within six months which can generate an improvement in metabolic factors.[16]

In this meta-analysis, we found that there was a reduction in BMI after intervention of 1500 mg cinnamon extract within 8-12 weeks. The mean BMI difference between the cinnamon and placebo groups was 0.21 kg/m^2, but it was not significantly different according to the analysis. This result could be caused by different including criteria for PCOS women in the two studies. Borzoei *et al.* declared a BMI 25-40 kg/m^2 as including criteria, but Hajimonfarednejad *et al.* declared a BMI $\geq$ 18 kg/m^2 as including criteria.[5,11] But Hajimonfarednejad *et al.* did not compare a multivariate of patients' characteristics, thus the risk of selection bias cannot be minimized. Hence, we did not assess for daily energy and macronutrient intake between the two groups.

Weight reduction could be associated with BMI itself. In this study, we showed a different result in weight reduction from BMI reduction in the two studies. Weight after treatment in the cinnamon group was higher than in the placebo group

(average = 1.08 kg), and it was not significant statistically. Although, the Borzoei *et al.* study showed a significant weight change in the cinnamon group (average 0.45 kg) after intervention, Hajimonfarednejad *et al.* did not show the same results due to different BMI criteria as including factors.[5,11] Hence, the different study criteria caused the different results.

Insulin resistance has an impact on the symptoms of PCOS such as increasing androgen level, menstrual irregularity, hyperglycemia and hyperlipidemia. Thus, controlling insulin resistance was recommended as one of the management targets of PCOS.[12] Cinnamon extract has been found to mitigate insulin resistance induced by high fructose diets and benefit glucose utilization by enhancing the insulin signalling pathway. Cinnamon extract increases glycogen synthesis by activating glycogen synthase and regulating insulin signalling thus it can improve insulin sensitivity. It can decrease absorption of glucose in the small intestine epithelium by enhancing glucosidase enzymes and inhibiting intestinal ATPase.[2,17] The polyphenolic component of cinnamon has insulin-like activity, such as quercetin, rutin, catechin, and kaempferol.[17] Significant heterogeneity was found for the four trials evaluating cinnamon for HOMA-IR ($I^2 = 84\%$, $p = 0.0003$) and effects were adjusted using the random effect model. Of 190 patients, there was 0.19 reduction in HOMA-IR after cinnamon intervention for eight to 24 weeks. This result was not significant statistically. No significant results can be caused when not all trials are adjusted for the characteristics of the participants.

Cinnamon regulates the blood sugar by stimulating insulin secretion from pancreas islets.[17] Cinnamon has a potential for reducing post-prandial intestinal glucose absorption by inhibiting the activity of enzymes involved in carbohydrate metabolism (pancreatic a-amylase and a-glycosidase).[12] It stimulates glucose metabolism and glycogen synthesis, inhibits gluconeogenesis by effects on key regulatory enzymes and motivates insulin release and insulin receptor activity, and increases Glucose transporter type 4 (GLUT-4) receptor synthesis. In animal studies, aqueous cinnamon extracts have been shown to increase the expression of peroxisome proliferator-activated receptors (PPARs), which are transcriptional factors involved in the regulation of HOMA-IR.[12] In this meta-analysis, we found no significant difference between fasting glucose in the cinnamon group and placebo. Administering 1500 mg cinnamon for 8-12 weeks can reduce glucose level by 4.8 mg/dl. We have controlled bias such as diabetes mellitus comorbid disease in this analysis, all diabetes mellitus and other metabolic diseases were excluded from the study.

Anderson *et al.* concluded that by consuming 500 mg cinnamon a day for two months, the level of fasting blood sugar, fasting insulin, and LDL-cholesterol increased in randomized controlled trials, however, HDL-cholesterol decreased in both groups (cinnamon and placebo groups).[18] In our systematic review, there were different results, in which only HDL-cholesterol and fasting blood sugar were significantly different between the two groups. This discrepancy is due to the different criteria of included studies. Khan *et al.* studied diabetes mellitus patients who had a metabolic disorder before the start of the study, while in our study most of the patients had a normal level of glucose and lipid profile. Besides, there was no dietary control for the subjects.[19]

Approximately 70% of women with recently diagnosed PCOS were shown to have borderline or high lipid levels, this included an increase in total cholesterol, triglyceride, LDL or a decrease in HDL levels. In a population study with median BMI 27 kg/m^2, 41% of patients with PCOS had HDL <1.29 mmol/L and 21% patients had triglyceride >1.68 mmol/L.[7] In registered studies, in patients with PCOS versus controls, a dyslipidemia diagnosis increased three times and anti-lipid prescription was two times higher in PCOS. In patients with PCOS the percentage treated with anti-lipids was, however, only 1.5%. Most women seek help for PCOS at a young age for irregular menses, hirsutism and concerns about infertility. It was previously reported that in those with a higher prevalence of smoking in PCOS versus controls that smoking in women with PCOS was related to increased adrenal responsiveness, a more adverse lipid profile and insulin resistance.[20-23] In this study we lacked any data for smoking habits and other exercise, which could potentially effect lipid profile.

Dehydroepiandrosterone sulfate (DHEA), is the most abundant steroid hormone in the circulation and has been used to induce PCOS in a mouse model.[2] The DHEA induced PCOS, with similar characteristics to humans such as hyperandrogenism, abnormal maturation of ovarian follicles and anovulation.[2] In this study, we showed that oral administration of cinnamon extract would reduce DHEA level (0.1 mcg/mL) after eight to 12 weeks. But this result was not significant.

Safety

From the latest systematic review about cinnamon adverse effects, it was concluded that cinnamon was safe to be used in a routine diet as a spice and/or flavoring agent. It is also well tolerated in controlled clinical settings. However, its use for medicinal purposes, in large doses or long duration, may lead to some adverse effects and it should be clinically monitored. There are no data for adverse effects in PCOS women. But, in diabetes mellitus and healthy subjects it can induce acute hepatitis, edema, stomatitis, and dermatitis, which can be relieved by symptomatic drugs or the cessation of

cinnamon administration.[24-27] It was reported that cinnamon extract equivalent to doses of 5-14 g of cinnamon powder did not alter alanine aminotransferase (ALT) and aspartate aminotransferase (AST), bilirubin and alkaline phosphatase.[28] The use of 1500 mg/dL of cinnamon powder for 12 weeks improved liver profile markers in patients with non-alcoholic fatty liver disease (NAFLD). ALT decreased by 26.6 IU/L, AST by 25.6 IU/L, gamma-glutamyltransferase (GGT) by 22.8 U/L and high sensitivity C-reactive protein (hs-CRP) by 2.9 mg/dL.[28,29] It also showed hepatoprotection against liver injury and lower liver fat in animal studies.[30,31] A phase I clinical trial of cinnamon showed no side effect including hepatotoxicity.[32]

Strength and limitation

This is the first systematic review and meta-analysis of double-blind RCTs. We analyzed the data based on PICO (using the same PCOS Rotterdam criteria) and found the same analysis to be reviewed. Authors analyzed the articles separately then discussed any discrepancies. However, our study had some limitations including different study duration and cinnamon dose in RCTs, different BMI of patients included in the study with some studies not adjusted for these discrepancies. Therefore, we need further studies to evaluate the effect of cinnamon for the same duration and dose, and thus we can provide better evidence for the efficacy of cinnamon in routine use for PCOS.

Conclusion

In conclusion, the present data suggest that cinnamon can improve fasting blood glucose, insulin level, HDL–cholesterol and menstrual cyclicity in PCOS women, but it did not affect weight, BMI, insulin resistance, triglyceride, LDL-cholesterol, total cholesterol and DHEA level. The effect of this herbal extract can be shown after 1000-1500 mg dose, administered for a minimum of eight weeks. Cinnamon can be a potential supplementary therapy agent for PCOS women.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'Cinnamon extract effects on insulin resistance, metabolic factors, and menstrual cyclicity of women with polycystic ovary syndrome: A systematic review and meta-analysis', https://doi.org/10.6084/m9.figshare.14716470.v1.[33]

Data are available under the terms of the Creative Commons Attributions 4.0 International license (CC-BY 4.0).

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