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OPEN PEER REVIEW

Evaluating the Efficacy of *Carum Copticum* Seeds on the Treatment of Patients with Nonalcoholic Fatty Liver Disease: A Multi-Center, Randomized, Triple–Blind, Placebo-Controlled Clinical Trial Study

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

4 comments · 16 Nov 2020 – 23 Nov 2020

Atefe Shabankare Reviewer

MINOR REVISION 16 Nov 2020

Overall, this is a clear, concise, and well-written manuscript. The introduction is relevant and has sufficient information about the previous study findings for readers to follow the present study's rationale and procedures.
The methods are generally appropriate, although clarification of a few details should be provided. Overall, the results are clear; more information about the efficacy of CC on grades of NAFLD just needs to be provided.

Referee 1 Reviewer

MAJOR REVISION 18 Nov 2020

Abstract section:

-Please write the full form of the abbreviation.
Introduction section:
-In the last part of the introduction, both sentences have the same meaning. Please merge them.

Methods and materials
In a clinical trial, you cannot use the prevalence formula to calculate the sample size. The sample size in this study should be calculated using the formula for comparing the means of one variable.
- Please recheck the flow diagram for the number of excluded patients, since the sum of the numbers of patients in the diagram was incorrect.
Results section
Please present one descriptive statistic: mean ± SD or median.
In table 1: please correct 51 ≥ in the age group and ≥111 for waist circumference.
-Please write the name of the statistical test used for the analysis in the table footnote.
-Please calculate the number needed to treat.
Discussion section:
-Please write the strengths and weaknesses of the study.
-Please write your suggestions for future studies.
-In the conclusion section, the authors recommend that such medication be added to the routine treatment protocol for NAFLD patients. Can this be concluded based on the results of one RCT?

General
-The manuscript should be prepared according to the journal format.
-English editing is necessary.
-Review the whole manuscript to correct words that are capitalized in the middle of sentences.

Associate Editor

MAJOR REVISION 20 Nov 2020

In this study, the authors have investigated the use of Ajwain in the treatment of NAFLD. They concluded that this herbal medicine is effective in the treatment of fatty liver disease. The topic is interesting, but the article needs to be improved. In addition to the reviewers' comments, my comments are as follows:

The manuscript must be revised by an English expert. For example: “The treatment group regarding to the placebo group showed significant change of total score of Leeds questioner , TG, ALT but for ALKP, AST, BMI despite the significant change found in both group but such increased as the same between two groups.” Or “on 90 grades 1 to 3 patients with NAFLD” or this sentence should be improved: “it is necessary to use some medicinal plants” or “On the contrary, “ or Has in “in HDL-C Has been associated” or immunological? Or “Fasting Blood Sugar: FBS, ALT and ALP liver enzymes (AST) , and lipid panel (Triglyceride: TG, Cholesterol: Chol, Low Density Lipoprotein: LDL, and High Density Lipoprotein: HDL)” “It is worth mentioning drug interactions, and possible side effects of drugs (sings of gastrointestinal, cutaneous, etc.) every third week.” “Tehran university of medical sciences, school of pharmacy” “Given the result of this study we can said” “CHOL or Chol?”

The introduction can be written better.

Reference? “few studies have focused on the medicinal effects of CCS on these patients”

The formula for sample size is n=((Z_(1-α/2)+Z_(1-β))^2 [P_1 (1-P_1)+P_2 (1-P_2)])/ 〖(P_1-P_2)〗 ^2

The inclusion criterion for age is different from the registered age range in IRCT.

Figure 2 is not self-explanatory.

Decrease or increase? And for which of them? “As it see in this table The treatment group regarding to the placebo group showed significant change of Leeds score, TG, ALT but for ALKP, AST, BMI despite the significant change found in both group but such increased as the same between two groups.”

Did the amount of ALKP increase after 8 weeks?

Is this true for FBS? “The cholesterol, FBS, HDL and LDL is not significant during time in both groups.”

This reference can be included in the discussion because it used a mixture of 4 herbal medicines, including Trachyspermum ammi: “Hormati A, Tooiserkany F, Mohammadbeigi A, Aliasl F, Moradi Dehnavi H. Effect of an Herbal Product on the Serum Level of Liver Enzymes in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized, Double-Blinded, Placebo-Controlled Trial, Iran Red Crescent Med J. 2019 ; 21(7):e91024. doi: 10.5812/ircmj.91024.”

I don’t think this deduction is logical: “Also, since NAFLD is associated with hypertension, as a component of the metabolic syndrome (37), Ajwain can be effective in treating NAFLD patients through its anti-hypertensive properties (9)”

Editor-in-Chief

MAJOR REVISION 23 Nov 2020

major revision

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Thank you for submitting your valuable manuscript to our journal. We would like to inform you that the peer review process of your manuscript is complete and requires "**Major Revision**". Although it has several useful points, it needs **Major Revision** to be reviewed again. Below you can find the abstracts of the peer review decision made by our editorial board members.

Reviewers' Comments:

Reviewer 1:
The subject of the manuscript is interesting, scientific and novel. It is well written and can attract the audience's attention. I recommend accepting it.

Thanks so lot

Reviewer 2:
Abstract section *:*
-Please write full name of abbreviation
The full name of abbreviation has been added in abstract

Introduction section:

-last part of the introduction, both sentences have the same meaning. Please merge them.

Now it is revised

Method and material

In clinical trial for calculating sample size , you cannot use the prevalence formula. Sample size in this study should be calculated by comparing the means of one variables formula.

Reply: The sample size formula has been corrected

The required sample size was estimated 90 patients (45 patients in each group) based on Shafiezadeh et al study (15) ($\overline{x} \pm SD$ in two group were -15.2±22 vs. -4.6±2.5), based on prevalence formula ($n = \left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2 \times \left(SD_1^2 + SD_2^2\right) / \left(\overline{x_1} - \overline{x_2}\right)^2$) with α=5%, β=30% and a dropout rate of 50%

- Please rechecked the follow diagram for number of excluded patients. Since according to the diagram the sum of number of patients was incorrect

Now it is revised

Results section

Please present one descriptive statistics mean± SD or median.

The median and IQR has been removed

In table 1: please correct 51 ≥ in age group and ≥111 waist circumference

Now it is revised

-please write the name of statistics test which used for the analysis in footnote of table

Now, the name of statistics test is write in footnote of table

-please calculate number needed to treatment.

The number needed to treat (NNT) in this study was 4.2. It means on average, 4.2 patients would have to receive experimental treatment (instead of control treatment) for one additional patient to have the study outcome.

Discussion section:

-Please write the strength and weakness of the study.

Now it is revised

-Please write your suggestion for futures studies.

Now it is revised

-In conclusion section, authors recommend that such medication added to the routine treatment protocol of NAFLD patients. According to results of one RCT, can it be concluded?

Now it is revised

General

-The manuscript should be prepared according to journal format.

The journal format has been checked

-English editing is necessary .

English garmmer has been done

-Review the whole manuscript for correcting the words which written in a capital letter in the middle of sentences.

It is checked

Reviewer 3:

overall, this is a clear, concise, and well-written manuscript. The introduction is relevant and has sufficient information about the previous study findings for readers to follow the present study rational and procedures.

The methods are generally appropriate, although clarification of a few details should be provided. Overall the results are clear just need to provide more information about efficacy of CC on grades of NAFLD.

The manuscript must be revised by an English expert. As example: "The treatment group regarding to the placebo group showed significant change of total score of Leeds questioner , TG, ALT but for ALKP, AST, BMI despite the significant change found in both group but such increased as the same between two groups."

Or "on 90 grades 1 to 3 patients with NAFLD"

or this sentence should be written better "it is necessary to use some medicinal plants"

or "On the contrary, "

or Has in "in HDL-C Has been associated"

or immunological?

Or "Fasting Blood Sugar: FBS, ALT and ALP liver enzymes (AST) , and lipid panel (Triglyceride: TG, Cholesterol: Chol, Low Density Lipoprotein: LDL, and High Density Lipoprotein: HDL)"

"It is worth mentioning drug interactions, and possible side effects of drugs (sings of gastrointestinal, cutaneous, etc.) every third week."

"Tehran university of medical sciences, school of pharmacy"

"Given the result of this study we can said"

"CHOL or Chol?"
Introduction can be written better.
Reference? "few studies have focused on the medicinal effects of CCS on these patients"

The above problems has been corrected

The formula for sample size is n=((Z_(1-α/2)+Z_(1-β))^2 [P_1 (1-P_1)+P_2 (1-P_2)])/〖(P_1-P_2)〗^2

Reply: The sample size formula has been corrected

The inclusion criterion for age is different from registered age range in IRCT

Now it is revised

Figure 2 is not self-representative.

Now it is revised

Decrease or increase? and for which of them? "As it see in this table The treatment group regarding to the placebo group showed significant change of Leeds score, TG, ALT but for ALKP, AST, BMI despite the significant change found in both group but such increased as the same between two groups.". Did the amount of ALKP increase after 8 weeks?

Due to the fact that ALPK changes in two groups and due to the assurance of laboratory tests for us in this study, the results related to ALPK has been removed.

Is it true for FBS? "The cholesterol, FBS, HDL and LDL is not significant during time in both groups."

Now it is revised

This reference can be included in discussion because of using a mixture of 4 herbal medicines includuing Trachyspermum ammi "Hormati A, Tooiserkany F, Mohammadbeigi A, Aliasl F, Moradi Dehnavi H. Effect of an Herbal Product on the Serum Level of Liver Enzymes in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized, Double-Blinded, Placebo-Controlled Trial, Iran Red Crescent Med J. 2019 ; 21(7):e91024. doi: 10.5812/ircmj.91024."

I don't think such deduction is logic "Also, since NAFLD is associated with hypertension, as a component of the metabolic syndrome (37), Ajwain can beeffective(helpful) *in treating NAFLD patients through its anti-hypertensive properties (9)"*

Now it is revised

2 Revision 1

2 comments · 10 Jan 2021 – 13 Jan 2021

Associate Editor

MINOR REVISION 10 Jan 2021

I reviewed the revised manuscript entitled " Evaluation of the Efficacy of Carum copticum Seeds on the Treatment of Patients with Nonalcoholic Fatty Liver Disease: A Multi-Center, Randomized, Triple–Blind, Placebo-Controlled Clinical Trial Study". Most of the concerns were addressed; however, a few concerns were not adequately addressed. The authors should follow the comments carefully and respond to them one by one so that the manuscript can be accepted for publication. Please find my comments below:

Abstract:
The results section needs to be improved.
NAFLD must be added after non-alcoholic fatty liver disease at its first mention, and then you can use it throughout the abstract. The same applies to Carum copticum seeds (CCS).
It is better to use the full form of each abbreviation at its first mention in the abstract, such as FBS, ALT, AST, WHR, TG. . ..

Introduction:
The last part of the introduction is repeated in Objectives.
5-10% of the weight? Mass? Surface? "It is also defined by the lipid accumulation of 5-10% in the liver tissue"
This item must be revised: "disorders of splenomegaly, jaundice, and ascites"
Carum copticum seeds (or Trachyspermum ammi) OR Carum copticum (Trachyspermum ammi) seeds?
"CCS is mostly cultivated in India" or "Carum copticum is mostly cultivated in India"?
What does immunologic mean in this sentence: "Ajwain contains numerous medicinal properties, including immunologic"?
Few studies have focused on investigating the medicinal effects of CCS on these patients (15, 16).
Two items numbered 5: 5-long-term hospitalization, and 5-not consumption alcohol,

Methods
Are there no data on the waist-hip ratio (WHR)?
It is better to delete (FD) from functional dyspepsia (FD).
These sentences can be merged: "Finally, a liver ultrasound was tested by a primary sonographer. It is worth noting that the Alpinion E-CUBE 15 EX ultrasound device (made in Korea) was used to assess liver ultrasound tests"
How did the authors prepare aqueous extracts of Ajwain seeds? At least a reference is needed.

Result:
What is the meaning of "the demographic data point of view"?
This is repeated in the abstract and results: "In the placebo group, the treatment group showed a significant change in the Leeds score, TG, and ALT. But a different situation has occurred for the AST and BMI. Despite a significant change was found in both groups, the amount of decrease was the same for the groups."
"In both groups, the cholesterol, FBS, HDL, and LDL are not significant during the time interval." But for FBS in the control group, the p-value is 0.015.

Discussion
This study was not a large study, and I think it is too early to conclude that "it is recommended that this kind of medication should be added to the routine treatment protocol in NAFLD patients."

What about ref 15? According to the literature survey, no study has investigated the effects of Ajwain on fatty liver.

Journal names in the references section must be in abbreviated form.

Editor-in-Chief MINOR REVISION 13 Jan 2021

minor revision

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Dr. Mohammad Gholami-Fesharaki,

Thank you for submitting your valuable manuscript to the journal. We would like to inform you that the peer review of your manuscript is now completed and despite several useful points, it needs "**Minor Revision**". Below you may find the peer review comments. Please reply to them one-by-one and re-submit it again.

Associate Editor's Comments:

Associate Editor 1:
I reviewed the revised manuscript entitled " Evaluation of the Efficacy of Carum copticum Seeds on the Treatment of Patients with Nonalcoholic Fatty Liver Disease: A Multi-Center, Randomized, Triple–Blind, Placebo-Controlled Clinical Trial Study". Most of the concerns were addressed however a few concerns were not considered accordingly. Authors should follow the comments carefully and respond to the comments one by one to accept the manuscript for publication. Please find my comments:

Abstract:
- The result section needs to be improved.

More numerical finding added in result abstract.

- NAFLD must be added to non-alcoholic fatty liver disease for the first time and then you can use it everywhere in abstract. It is also true for Carum copticum seeds (CCS).
***Reply*: OK**
- It is better to use the full name of abbreviation in the abstract for the first time like FBS, ALT, AST, WHR, TG =
Reply: The full name of abbreviation has been added

Introduction:
- Last part of the introduction is repeated in Objectives.=
Reply: repeated section removed

- 5-10% weight? Mass? Surface? "It is also defined by the lipid accumulation of 5-10% in the liver tissue"= ***Reply: Now it is revised***

- This item must be revised "disorders of splenomegaly, jaundice, and ascites"

- Carum copticum seeds (or Trachyspermum ammi) OR Carum copticum (Trachyspermum ammi) seeds? = ***Reply: Now it is revised***

- "CCS is mostly cultivated in India" or Carum copticum is mostly cultivated in India

*= **Reply:Now it is revised***
- What did immunologic mean in this sentence "Ajwain contains numerous medicinal properties, including immunologic"
Reply**: **In reference 37 It has been explained= Antiinflammatory, antioxidant, and immunological effects of Carum copticum L. and some of its constituents

*- few studies have focused on investigating the medicinal effects of CCS on these patients (15, 16)= **Reply**: **OK***
- Two 5: 5-long-term hospitalization, and 5-not consumption alcohol
Reply** :**Now it is revised

Methods
- There is not any data about waist-hip ratio (WHR)?
Reply**: **How to calculate WHR and BMI was written
- It is better to delete (FD) in functional dyspepsia (FD).
Reply**: **FD removed

*- These sentences can be merged. "Finally, a liver ultrasound was tested by a primary sonographer. It is worth noting that the Alpinion E-CUBE 15 EX ultrasound device (made in Korea) was used to assess liver ultrasound tests"= **Reply**: **The above sentences were merged***

*- How did the authors prepare aqueous extracts of Ajwain seeds? At least, it needs a reference. **Reply**: **How to extract and relevant reference was mentioned***

Result:
*- What is the meaning of"the demographic data point of view"?=**Now it revised.***

- It is repeated in abstract and result. "In the placebo group, the treatment group showed a significant change in the Leeds score, TG, and ALT. But a different situation has occurred for the AST and BMI. Despite a significant change was found in both groups, the amount of decrease was the same for the groups."
*"In both groups, the cholesterol, FBS, HDL, and LDL are not significant during the time interval." But about FBS in control group, p value is 0.015==**Now it revised.***

Discussion
*This study was not a big study and I think it is too early to conclude "it is recommended that this kind of medication should be added to the routine treatment protocol in NAFLD patients."= **Reply**: **This sentence was deleted***

*- How about ref 15? According to the literature survey, no study has investigated the effects of Ajwain on the fatty liver= **Reply**: **ref 15 was added***

- Journal name in references section must be in abbreviated form.=
Reply**: **The abbreviated form of the journal name was mentioned in the references section

3 Revision 2

1 comment · 23 Jan 2021

Editor-in-Chief

ACCEPT 23 Jan 2021

Accept