Nama Jurnal **: Journal Traditional and Complementary Medicines (JTCM)**

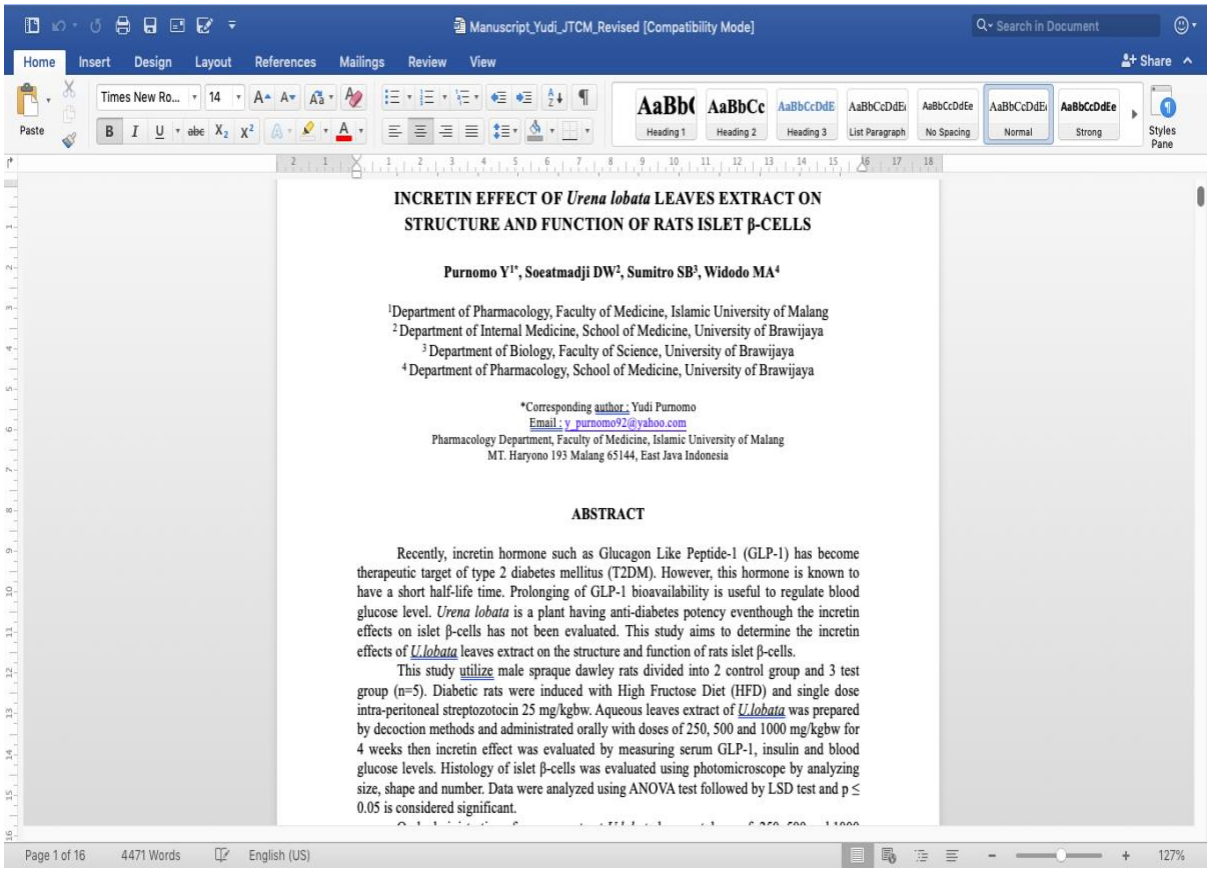
Indeks **: Scopus (Q1), SJR (0.76)**

https://www.sciencedirect.com/science/article/pii/S2225411016302802

Judul Artikel : Incretin effect of *Urena lobata* leaves extract on structure and function of rats islet β-cells

Tanggal	Activity	Reviewer Comments
16-05-2016	Submision of article	
16-05-2016	Article received	Article has been received by editor
01-06-2016	Editor responses	Comments editor were attached
01-06-2016	Reviewer comments	Comments from reviewer were attached
22-08-2016	Resubmit the revised article	Author responses to reviewer were attached
25-10-2016	Editor responses	The article accepted
28-10-2016	Editor responses	The article will be published
16-11-2016	Galley proof sending	Galley proof correction
27-11-2016	Resubmit the revised article	-
12-07-2017	Published	On line published

Manuscript submission :



Manuscript_Yudi_JTCM_Revised [Compatibility Mode]

INCRETIN EFFECT OF *Urena lobata* LEAVES EXTRACT ON STRUCTURE AND FUNCTION OF RATS ISLET β-CELLS

Purnomo Y[1*], Soeatmadji DW[2], Sumitro SB[3], Widodo MA[4]

[1]Department of Pharmacology, Faculty of Medicine, Islamic University of Malang
[2]Department of Internal Medicine, School of Medicine, University of Brawijaya
[3]Department of Biology, Faculty of Science, University of Brawijaya
[4]Department of Pharmacology, School of Medicine, University of Brawijaya

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MT. Haryono 193 Malang 65144, East Java Indonesia

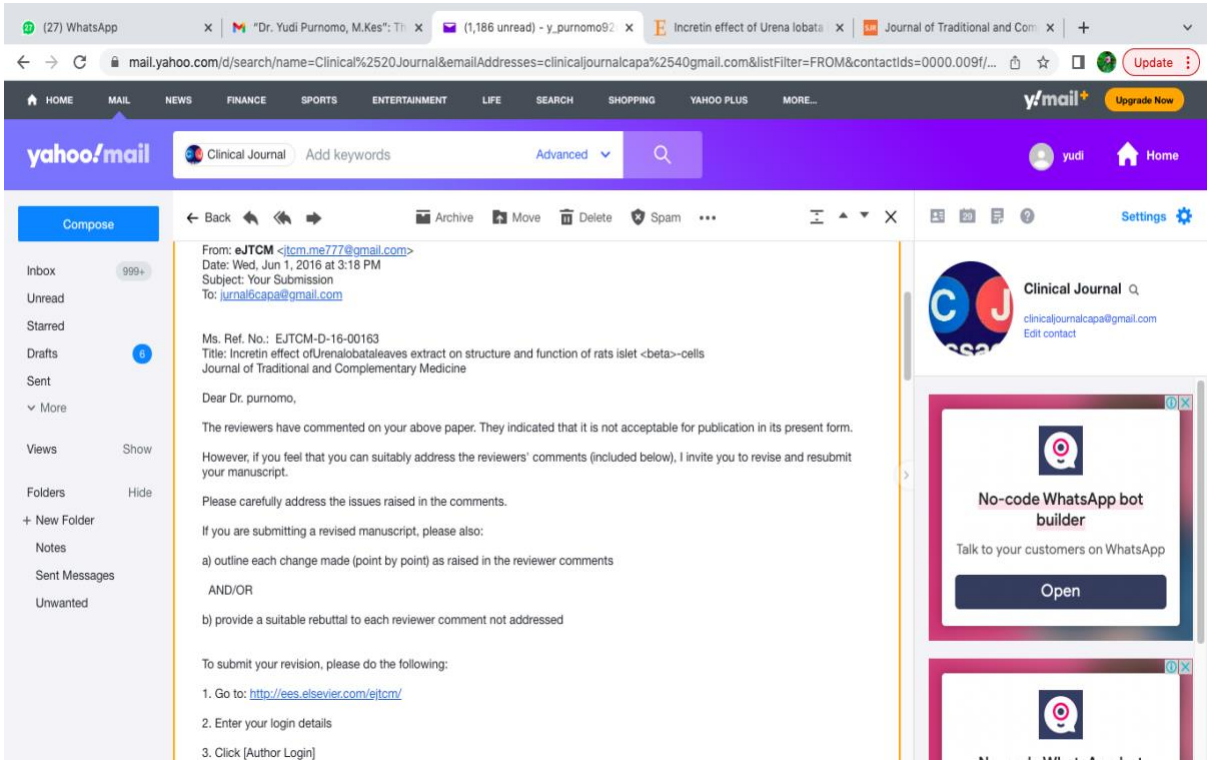
ABSTRACT

Recently, incretin hormone such as Glucagon Like Peptide-1 (GLP-1) has become therapeutic target of type 2 diabetes mellitus (T2DM). However, this hormone is known to have a short half-life time. Prolonging of GLP-1 bioavailability is useful to regulate blood glucose level. *Urena lobata* is a plant having anti-diabetes potency eventhough the incretin effects on islet β-cells has not been evaluated. This study aims to determine the incretin effects of *U.lobata* leaves extract on the structure and function of rats islet β-cells.

This study utilize male spraque dawley rats divided into 2 control group and 3 test group (n=5). Diabetic rats were induced with High Fructose Diet (HFD) and single dose intra-peritoneal streptozotocin 25 mg/kgbw. Aqueous leaves extract of *U.lobata* was prepared by decoction methods and administrated orally with doses of 250, 500 and 1000 mg/kgbw for 4 weeks then incretin effect was evaluated by measuring serum GLP-1, insulin and blood glucose levels. Histology of islet β-cells was evaluated using photomicroscope by analyzing size, shape and number. Data were analyzed using ANOVA test followed by LSD test and $p \leq 0.05$ is considered significant.

Page 1 of 16 4471 Words English (US) 127%

Editor comments :



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Date: Wed, Jun 1, 2016 at 3:18 PM
Subject: Your Submission
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Ms. Ref. No.: EJTCM-D-16-00163
Title: Incretin effect ofUrenalobataleaves extract on structure and function of rats islet <beta>-cells
Journal of Traditional and Complementary Medicine

Dear Dr. purnomo,

The reviewers have commented on your above paper. They indicated that it is not acceptable for publication in its present form.

However, if you feel that you can suitably address the reviewers' comments (included below), I invite you to revise and resubmit your manuscript.

Please carefully address the issues raised in the comments.

If you are submitting a revised manuscript, please also:

a) outline each change made (point by point) as raised in the reviewer comments

AND/OR

b) provide a suitable rebuttal to each reviewer comment not addressed

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Reviewer comments

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3. Click [Author Login]
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4. Click [Submissions Needing Revision]
I look forward to receiving your revised manuscript.

Yours sincerely,

Lee-Yen Sheen
Editor in Chief
Journal of Traditional and Complementary Medicine

Reviewers' comments:

Reviewer #1: Comments:
The study is an interesting one and publishable in a reputable journal of such, but I think the following comments will enrich the outreach of the work and convey the intended information to readers, also making it reproducible.
Introduction:
1. The first sentence could be recast as "Modulation of incretins in the treatment of type 2 diabetes mellitus have received increasing attention attention in the recent search for potent anti-diabetes".
2. Hormone(s) (not hormon(s)).
3. Hyperglycemia (Not hyperglycemic) in the first two paragraphs.
4. Incretin hormone especially GLP-1 has effect to cure T2DM patient. ? This is not a clear sentence.
5. I think the authors should reconstruct the information in the second and third paragraphs to flow.
6. Therapy (not theraphy)
7. I think the sentence "Herbs is one of medication choices because they have less side effect and holistic care property", can be replaced with "Herbs are becoming popular medications of choice in the managements of diseases

due to their perceived less side effects …"
8. I think the sentence "One of traditional plants which have anti-diabetic effect is Caesar weed (Urenalobata)" Should be expunged, or authors could move to the body of the same paragraph with relevant ref if they wish to retain.
9. The authors may find it required to redraft the last sentences, focusing on U. lobota and its reported efficacies in the literature.

Material and Methods:

1. Authors should carefully edit this section for minor typographical mistakes.
2. Animals and Treatments (The study was conducted). I think not they were conducted
3. P≤0.05 or P<0.05 was considered to be statistical significant (I think you used 95% CI)

Grouping and Treatments:

1. You did not state anywhere in the methodology (abstract and body), if you firstly induced diabetes in the U lobota extract treated animals.
2. It is stated in your abstract that the animals were divided into 2 control groups and 3 test goups. Diabetic rats were induced with High Fructose Diet (HFD) and single dose intra-peritoneal streptozotocin. Aqueous leaves extract of U. lobata was administrated orally with doses of 250, 500 and 1000mg/kgbw for 4 weeks (?).
3. In the methods section, it is written "For eight weeks, the normal group (NG) received ND whereas the diabetic (DG) and treatment groups received HFD. The treatment groups were given aqueous extract of U. lobata (AEU) at a dose of250 mg/kg, 500 mg/kg, and 1000 mg/kgbw for four weeks (?)."

Results, discussion, conclusion and infrences:

I think statements below written before the results will be a repetition of the legends and can be expunged "Body weight, food consumption, blood glucose and insulin level of diabetic rat supplementedwith U.lobataleaf extract can be shown Table 1." "GLP-1 serum level of diabetic rat supplemented withU.lobata leaf extract can be shown Figure 1." "Insulin serum level of diabeticrat supplemented withU.lobata leaf extractcan be shown at Figure 2." "Blood glucose level of rat supplemented with U.lobata after stimulating glucose oral can be shown at Figure 3." "Islet <beta>-cellswere observed under microscope at 400x magnification as shown at Figure 4."

The treatment groups includes
Normal group
Diabetic group
EAU-250 mg/kg bw
EAU-500 mg/kg bw
EAU-1000 mg/kg bw

1. If these are your treatments, without pre-induction of diabetes in the EAU treated groups, do you not think that the EAU affecting both Serum Insulin level, Blood glucose level, GLP-1, body weight and food consumption when compared with the normal control animals, in the same way like the diabetic groups.
2. I think these results are fantastic if only it is clear that, the EAU are pre-induced diabetes.
3. What do the authors think may be responsible for the low GLP-1 level in the diabetic rats, knowing that the Secretagogues of GLP-1 is nutrition, and there is high food consumption in the rats.

4. Please, redefine the # in table 1, as it also indicate significant difference in your treatment groups to both the control and the diabetic in the Food consumption results.
5. There is need to define the superscripts (a, b, c and d) as presented in tables 2, 3 and 4.
6. I don't think it is also necessary to present a single result as table and figure (as of GPI-1, insulin and blood glucose levels).

Representative photomicrographs:

1. Why is the EAU-250 mg/kg bw not represented
2. The authors used the verb "PREVENT" in defining the activities of EAU in the discussion and conclusion.
3. If it is clear that EAU was administered before inducing diabetes, then they are 100% correct. But if diabetes induction precedes EAU treatments, I suggest they use "AMELIORATE".

These observations are intended to better the presentation of the work.

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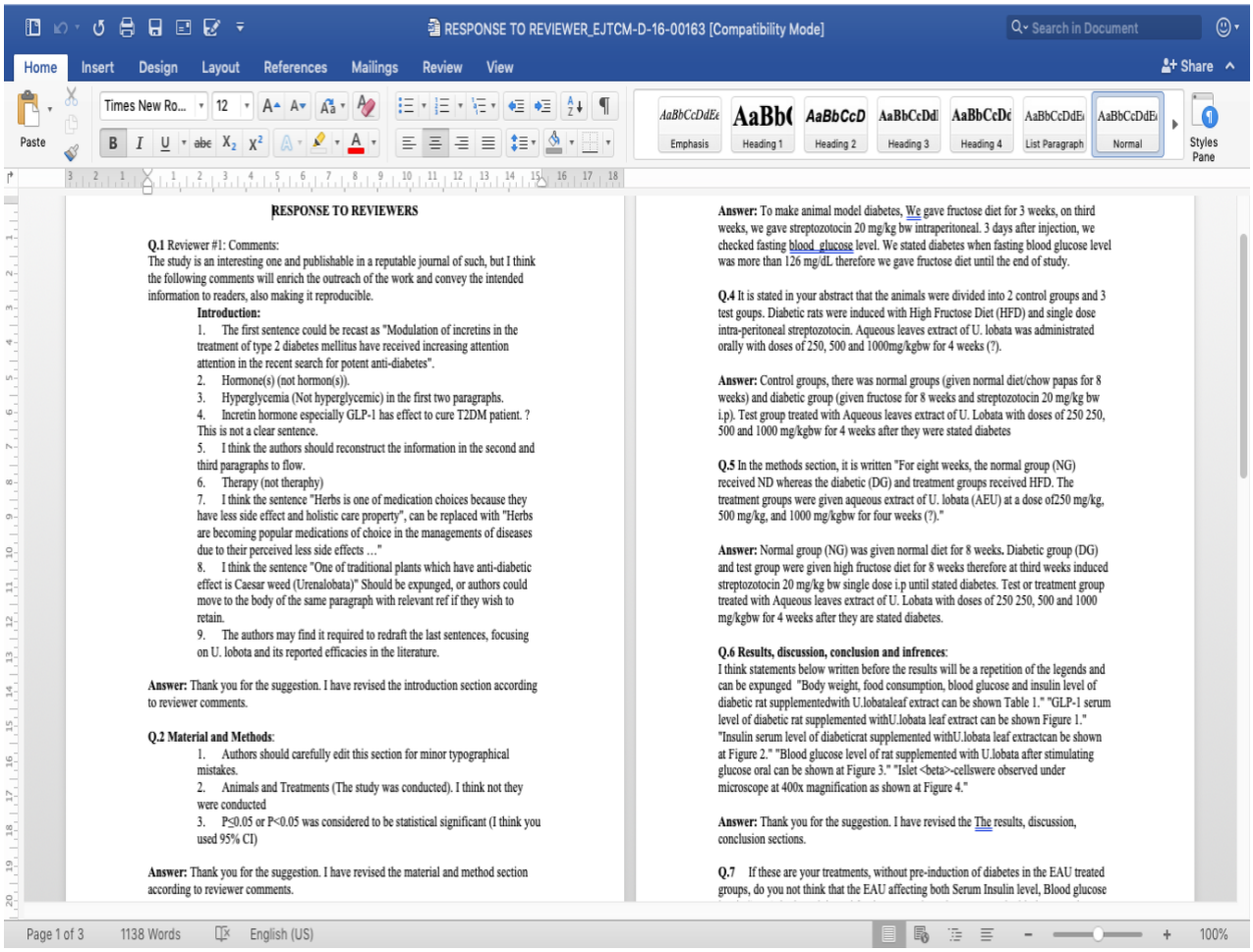
Response to reviewer :



RESPONSE TO REVIEWER_EJTCM-D-16-00163 [Compatibility Mode]

RESPONSE TO REVIEWERS

Q.1 Reviewer #1: Comments:
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9. The authors may find it required to redraft the last sentences, focusing on U. lobota and its reported efficacies in the literature.

Answer: Thank you for the suggestion. I have revised the introduction section according to reviewer comments.

Q.2 Material and Methods:

1. Authors should carefully edit this section for minor typographical mistakes.
2. Animals and Treatments (The study was conducted). I think not they were conducted
3. P≤0.05 or P<0.05 was considered to be statistical significant (I think you used 95% CI)

Answer: Thank you for the suggestion. I have revised the material and method section according to reviewer comments.

Answer: To make animal model diabetes, We gave fructose diet for 3 weeks, on third weeks, we gave streptozotocin 20 mg/kg bw intraperitoneal. 3 days after injection, we checked fasting blood glucose level. We stated diabetes when fasting blood glucose level was more than 126 mg/dL therefore we gave fructose diet until the end of study.

Q.4 It is stated in your abstract that the animals were divided into 2 control groups and 3 test goups. Diabetic rats were induced with High Fructose Diet (HFD) and single dose intra-peritoneal streptozotocin. Aqueous leaves extract of U. lobata was administrated orally with doses of 250, 500 and 1000mg/kgbw for 4 weeks (?).

Answer: Control groups, there was normal groups (given normal diet/chow papas for 8 weeks) and diabetic group (given fructose for 8 weeks and streptozotocin 20 mg/kg bw i.p). Test group treated with Aqueous leaves extract of U. Lobata with doses of 250 250, 500 and 1000 mg/kgbw for 4 weeks after they were stated diabetes

Q.5 In the methods section, it is written "For eight weeks, the normal group (NG) received ND whereas the diabetic (DG) and treatment groups received HFD. The treatment groups were given aqueous extract of U. lobata (AEU) at a dose of250 mg/kg, 500 mg/kg, and 1000 mg/kgbw for four weeks (?)."

Answer: Normal group (NG) was given normal diet for 8 weeks. Diabetic group (DG) and test group were given high fructose diet for 8 weeks therefore at third weeks induced streptozotocin 20 mg/kg bw single dose i.p until stated diabetes. Test or treatment group treated with Aqueous leaves extract of U. Lobata with doses of 250 250, 500 and 1000 mg/kgbw for 4 weeks after they are stated diabetes.

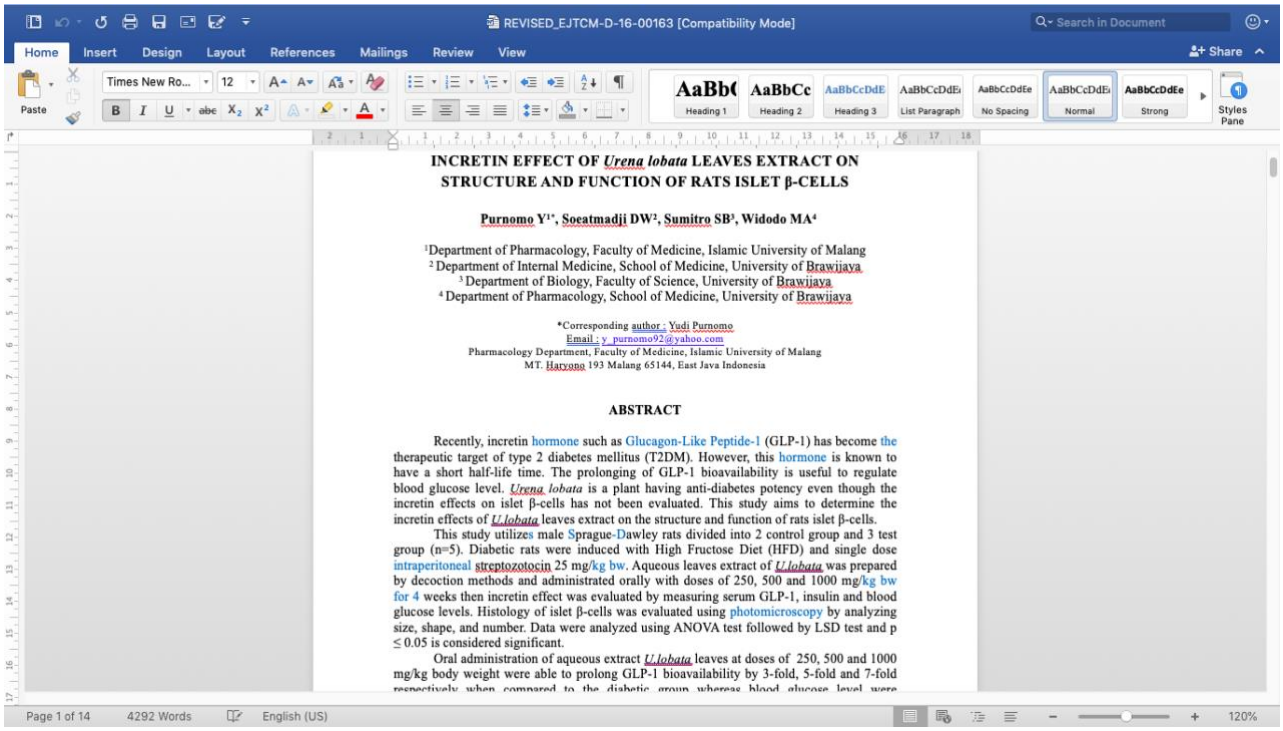
Q.6 Results, discussion, conclusion and infrences:
I think statements below written before the results will be a repetition of the legends and can be expunged "Body weight, food consumption, blood glucose and insulin level of diabetic rat supplementedwith U.lobataleaf extract can be shown Table 1." "GLP-1 serum level of diabetic rat supplemented withU.lobata leaf extract can be shown Figure 1." "Insulin serum level of diabeticrat supplemented withU.lobata leaf extractcan be shown at Figure 2." "Blood glucose level of rat supplemented with U.lobata after stimulating glucose oral can be shown at Figure 3." "Islet <beta>-cellswere observed under microscope at 400x magnification as shown at Figure 4."

Answer: Thank you for the suggestion. I have revised the The results, discussion, conclusion sections.

Q.7 If these are your treatments, without pre-induction of diabetes in the EAU treated groups, do you not think that the EAU affecting both Serum Insulin level, Blood glucose

Page 1 of 3 1138 Words English (US) 100%

Revised article :



REVISED_EJTCM-D-16-00163 [Compatibility Mode]

INCRETIN EFFECT OF *Urena lobata* LEAVES EXTRACT ON STRUCTURE AND FUNCTION OF RATS ISLET β-CELLS

Purnomo Y[1]*, Soeatmadji DW[2], Sumitro SB[3], Widodo MA[4]

[1]Department of Pharmacology, Faculty of Medicine, Islamic University of Malang
[2] Department of Internal Medicine, School of Medicine, University of Brawijaya
[3] Department of Biology, Faculty of Science, University of Brawijaya
[4] Department of Pharmacology, School of Medicine, University of Brawijaya

*Corresponding author : Yudi Purnomo
Email : y_purnomo92@yahoo.com
Pharmacology Department, Faculty of Medicine, Islamic University of Malang
MT. Haryono 193 Malang 65144, East Java Indonesia

ABSTRACT

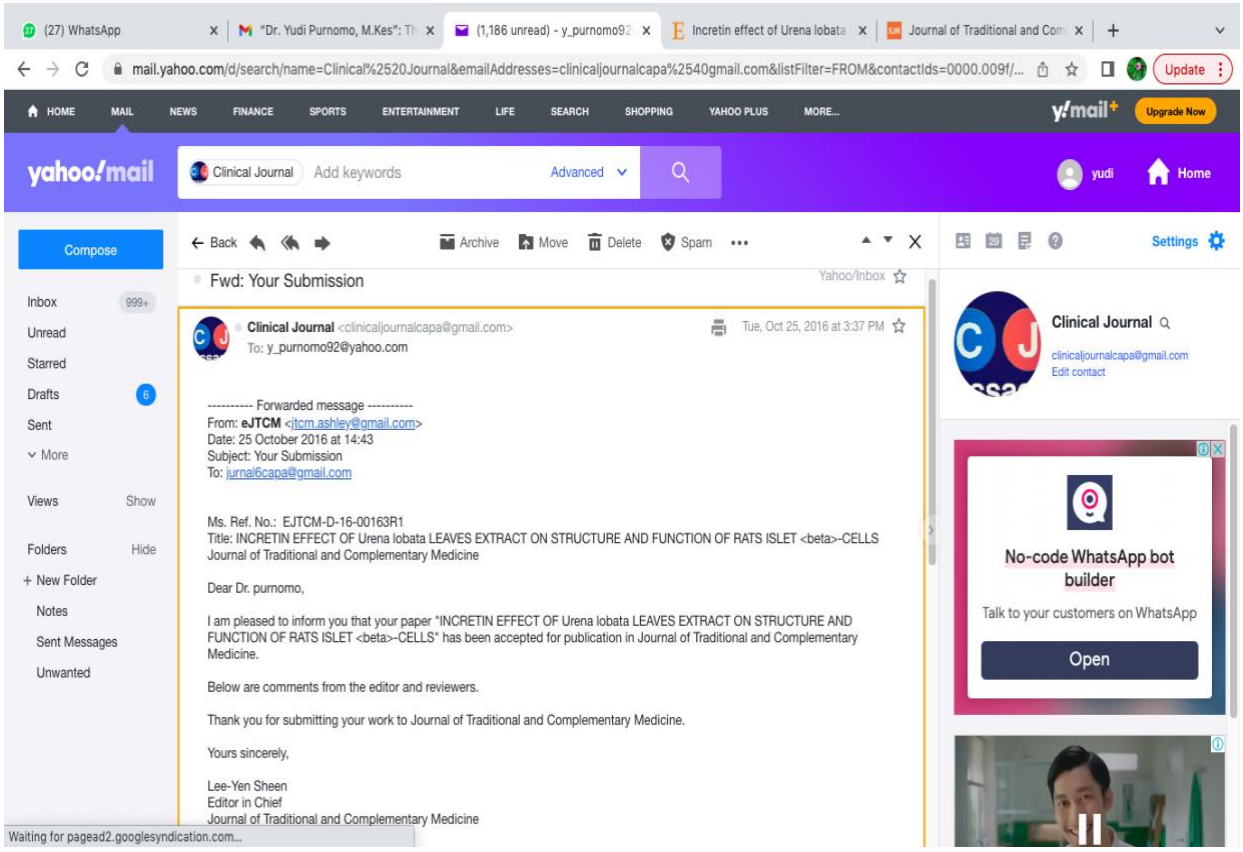
Recently, incretin hormone such as Glucagon-Like Peptide-1 (GLP-1) has become the therapeutic target of type 2 diabetes mellitus (T2DM). However, this hormone is known to have a short half-life time. The prolonging of GLP-1 bioavailability is useful to regulate blood glucose level. *Urena lobata* is a plant having anti-diabetes potency even though the incretin effects on islet β-cells has not been evaluated. This study aims to determine the incretin effects of *U.lobata* leaves extract on the structure and function of rats islet β-cells.

This study utilizes male Sprague-Dawley rats divided into 2 control group and 3 test group (n=5). Diabetic rats were induced with High Fructose Diet (HFD) and single dose intraperitoneal streptozotocin 25 mg/kg bw. Aqueous leaves extract of *U.lobata* was prepared by decoction methods and administrated orally with doses of 250, 500 and 1000 mg/kg bw for 4 weeks then incretin effect was evaluated by measuring serum GLP-1, insulin and blood glucose levels. Histology of islet β-cells was evaluated using photomicroscopy by analyzing size, shape, and number. Data were analyzed using ANOVA test followed by LSD test and $p \leq 0.05$ is considered significant.

Oral administration of aqueous extract *U.lobata* leaves at doses of 250, 500 and 1000 mg/kg body weight were able to prolong GLP-1 bioavailability by 3-fold, 5-fold and 7-fold respectively when compared to the diabetic group whereas blood glucose level were

Page 1 of 14 4292 Words English (US) 120%

Editor responses : (Accepted)



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Ms. Ref. No.: EJTCM-D-16-00163R1
Title: INCRETIN EFFECT OF Urena lobata LEAVES EXTRACT ON STRUCTURE AND FUNCTION OF RATS ISLET <beta>-CELLS
Journal of Traditional and Complementary Medicine

Dear Dr. purnomo,

I am pleased to inform you that your paper "INCRETIN EFFECT OF Urena lobata LEAVES EXTRACT ON STRUCTURE AND FUNCTION OF RATS ISLET <beta>-CELLS" has been accepted for publication in Journal of Traditional and Complementary Medicine.

Below are comments from the editor and reviewers.

Thank you for submitting your work to Journal of Traditional and Complementary Medicine.

Yours sincerely,

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Article reference: JTCME165
Journal title: Journal of Traditional and Complementary Medicine
Corresponding author: Dr. yudi purnomo
First author: Dr. yudi purnomo

Dear Dr. purnomo,

Your article INCRETIN EFFECT OF Urena lobata LEAVES EXTRACT ON STRUCTURE AND FUNCTION OF RATS ISLET <beta>-CELLS will be published in Journal of Traditional and Complementary Medicine.

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Editor comments : Galley proof correction

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Article reference: JTCME_EJTCM-D-16-00163
Article title: INCRETIN EFFECT OF Urena lobata LEAVES EXTRACT ON STRUCTURE AND FUNCTION OF RATS ISLET <beta>-CELLS
To be published in: Journal of Traditional and Complementary Medicine
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Original Article

Incretin effect of *Urena lobata* leaves extract on structure and function of rats islet β-cells

Y. Purnomo [a, *], D.W. Soeatmadji [b], S.B. Sumitro [c], M.A. Widodo [d]

[a] Department of Pharmacology, Faculty of Medicine, Islamic University of Malang, Indonesia
[b] Department of Internal Medicine, School of Medicine, University of Brawijaya, Indonesia
[c] Department of Biology, Faculty of Science, University of Brawijaya, Indonesia
[d] Department of Pharmacology, School of Medicine, University of Brawijaya, Indonesia

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Keywords:
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ABSTRACT

This study aims to determine the incretin effects of *Urena lobata* leaves extract on the structure and function of rats islet β-cells. This study utilizes male Sprague-Dawley rats divided into 2 control group and 3 test group (n = 5). Diabetic rats were induced with High Fructose Diet (HFD) and single dose intra-peritoneal streptozotocin 25 mg/kg bw. Aqueous leaves extract of *U. lobata* was prepared by decoction methods and administrated orally with doses of 250, 500, and 1000 mg/kg bw for 4 weeks then incretin effect was evaluated by measuring serum GLP-1, insulin, and blood glucose levels. Histology of islet β-cells was evaluated using photomicroscopy by analyzing size, shape, and number. Data were analyzed using ANOVA test followed by LSD test and $p \leq 0.05$ is considered significant. Oral administration of aqueous

Final version Published on line :