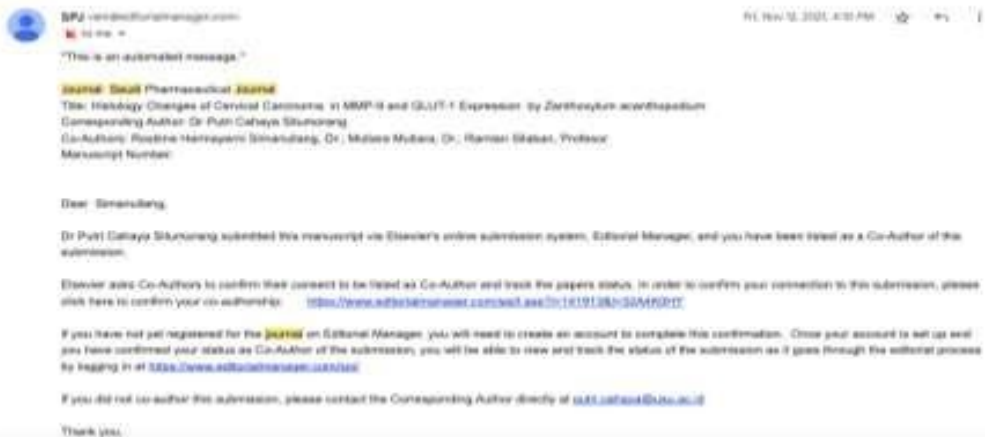
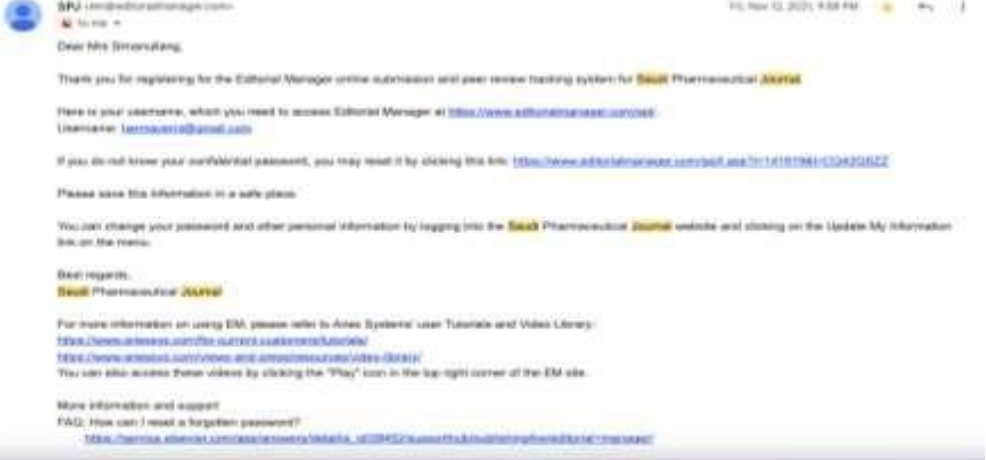




Judul		Histological changes of cervical tumours following Zanthoxylum acanthopodium DC treatment, and its impact on cytokine expression
Nama Jurnal/Volume/issu/Hal		Saudi Journal of Biological Sciences 29 (4), 2706-2718
Peran		Author
No	Tanggal	Keterangan
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2	01-11-21	Konfirmasi semua author dan co-author
3	02-11-21	Permintaan pihak jurnal melengkapi semua data-data auhtor dan co-author
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6	16-11-21	Permintaaan kembali untuk revisi
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10	04-01-22	Published

Bukti Korespondensi

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06-11-21	<p>Saudi Journal of Biological Sciences - em@editorialmanager.com Sat, Nov 6, 2021, 2:45 PM</p> <p>"This is an automated message."</p> <p>Journal: Saudi Journal of Biological Sciences Title: The Cytokines Expression on Histological Changes of Cervical Cancer by Zanthoxylum acanthopodium Corresponding Author: Dr Putri Cahaya Simanungang Co-Authors: Ruzlinda Hermayanti Simanungang, Marisa Harisa, Dr. Nuradina Nuradina, S Ray, Ms. M.Pd, Bernita Ghazali, S Ray, Ms. M.Stanley, Saida Surya Manurung, S.Ray, Ms. M.Ray Manuscript Number:</p> <p>Dear Ruzlinda Hermayanti Simanungang,</p> <p>Dr Putri Cahaya Simanungang submitted this manuscript via Elsevier's online submission system, Editorial Manager, and you have been listed as a Co-Author of this submission.</p> <p>Elsevier asks Co-Authors to confirm their consent to be listed as Co-Author and track the papers status. In order to confirm your connection to this submission, please click here to confirm your co-authorship:</p> <p>https://www.editorialmanager.com/sjbs/author.asp?AUTH=342404&X=03WL3LT</p> <p>If you have not yet registered for the SJBS on Editorial Manager, you will need to create an account to complete this confirmation. Once your account is set up and you have confirmed your status as Co-Author of the submission, you will be able to view and track the status of the submission as it goes through the editorial process by logging in at https://www.editorialmanager.com/sjbs/</p> <p>If you did not co-author this submission, please contact the Corresponding Author directly at jadriahayati@unswin.ac.id</p> <p>Thank you.</p>

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No	Part or Question	Reviewer Comments	Author response
Reviewer 1			
1.	Question 1	Question 1: Why did the authors choose the doses 100, 200 and 400 mg/kg of the plant extract?	<p>We used this dose based on a previous study by one of our authors entitled "Acute toxicity test and histological description of organs after giving nano herbal andaliman (<i>Zanthoxylum acanthopodium</i>)" with the results of the toxicity test that andaliman has a low toxic value (LD50 of 9.807g /KgBW \pm 0.075). In addition, the use of these doses has been carried out in previous studies, with the results that Andaliman fruit extract in the dose of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW have analgesic effectivity more than 50% compared to mefenamic acid with effectivity. of 93.16%, 89.21%, and 112.01% respectively. Conclusion: Andaliman fruit extract is an effective analgesic.</p> <p>We cite the link below http://ojs.udb.ac.id/index.php/infokes/article/view/1299)</p>
2	Question 2	Question 2: Why did the authors choose the methanolic extract to conduct the experiments?	<p>The methanol extract was able to identify 20 chemical compounds in the methanolic extract of <i>Z. acanthopodium</i> fruit. Sixteen chemical compounds derived from terpenes and terpenoids. Four other chemical compounds were structurally identified as aliphatic derivatives (neoherculin; ethyl linoleate; ethanol, 2-(3,3-dimethylcyclohexylidene)-; and 9,12-Octadecadienoyl chloride). Qualitative phytochemical analysis of andaliman fruit extract with water, methanol, ethyl acetate, and hexane showed that the phytochemical content was not lost in the methanol extract. In contrast to the andaliman fruit in water solvents, ethyl acetate and hexane.</p> <p>You cant find in this link https://www.smujo.id/biodiv/article/view/6464/4202 and https://iopscience.iop.org/article/10.1088/1755-1315/122/1/012089/pdf</p>

3	Question 3	<p>Question 3: It is difficult to publish articles about plant extract without analyzing its constituents. Did the authors analyze the constituents of the plant extract that was used in their study? If yes, please refer to these constituents. If not, please conduct this step by sending the extract to a laboratory of analysis.</p>	<p>Authors have analyzed the constituents of the plant extract that was used in this study. Andaliman fruit extracts contain various bioactive compounds such as alkaloids, flavonoids, glycosides, saponins, tannins, triterpene/steroids and glycoside anthraquinone. We do not include these data in this manuscript because our results are the same as those of other authors. So we just cite it to avoid plagiarism.</p> <p>You can find in this link https://www.smujo.id/biodiv/article/view/6464/4202 and https://iopscience.iop.org/article/10.1088/1755-1315/122/1/012089/pdf</p>
4	Question 4	<p>Question 4: How did the authors confirm that the model of cervical cancer was successfully established after the injection of benzopyrene 50 mg/BW?. The authors need to explain this information clearly in the section of methods.</p>	<p>We used 50mg of B[a]P for cervical induction, based on a previous study (Sanchala, D., Bhatt, LK, Pethe, P., Shelat, R., & Kulkarni, YA 2018. Anticancer activity of methylene blue via inhibition of heat shock protein 70. Biomedicine & Pharmacotherapy, 107, 1037–1045. doi:10.1016/j.biopha.2018.08.095). However, in the Wistar strain rats, tumours began to appear after 3 months.</p> <p>We have revised it in the material and methods section.</p>
5	Question 5	<p>Question 5: There is variability in the effect of different doses of the plant extract on SOD, MDA and NGAL. Sometimes, the lower or middle dose produces an effect and sometimes the higher dose produces the effect. Can the authors provide explanation for these findings?</p>	<p>SOD: SOD levels in cancer rats given ZAM were significant at doses of 100 and 200 mg/kgBW compared to the C+ group and decreased with increasing doses.</p> <p>MDA: MDA levels showed a significant difference at doses of 200 and 400 mg/kg compared to the C+ group. The decrease in MDA levels was in line with the increase in the ZAM dose.</p> <p>NGAL: NGAL levels are significant only at a dose of 400mg/kgBW.</p> <p>Based on the biochemical data of SOD, MDA, and NGAL in cancer rats, it is known that there are significant differences. SOD levels were significant at doses of ZAM 100 and 200 mg/Kg</p>

			<p>BW, MDA levels, 200 and 400 mg/Kg BW and NGAL levels were only significant at doses of 400mg/kgBW compared to the C+ group. Antioxidants found in andaliman can lower levels of MDA and serum NGAL, thereby increasing SOD activity. By increasing SOD activity as a result of ZAM administration, it is possible to protect cells from oxidant disorders and oxidative stress, which can lead to a variety of diseases, including cancer. In cervical cancer, increased lipid peroxide due to antioxidant deficiency was associated with increased levels of Malondialdehyde (MDA) and circulating neutrophil gelatinase associated lipocalin (NGAL) and decreased Superoxide dismutase (SOD) activity (Sherif. et al., 2018; Thakur et al. ., 2015). Furthermore, elevated MDA levels in tumor tissue may be associated with SOD deficiency. If this continues, superoxide anion accumulates, which is highly radical and capable of penetrating membranes, causing negative effects far from the tumor (Sherif. et al., 2018).</p>
6	Question 6	<p>Question 6: You can not represent figure 1 in this way. Before treatment, you cannot name the groups as C+, ZAM.....etc because the animals didn't receive the treatments yet. Make a percentage body weight change from the 2 figures and represent the figures as one figure instead of figures 1a and 1b.</p> <p>Also, by looking at figure 1b, I doubt that there is significant difference between C and C+ groups. Check the statistical analysis and indicate the number of animals in each group.</p>	<p>Thank you for your advice, We have revised it</p>
7	Question 7	<p>Question 7: The authors cannot simply weigh the cervical organs and conclude that the weight in cervical organs represents the weight of cervical cancer. It could be, but not necessarily, an indicative. Please give explanation.</p>	<p>Thank you for your advice, We have revised it.</p> <p>We have changed the statement from "weight of cervical cancer" to "weight in cervical organs after being given andaliman".</p>
General comments			

8	The title, abstract and introduction	The authors need to put the full botanical or authority name of the plant (<i>Zanthoxylum acanthopodium</i> DC.) in its first appearance in the title, abstract and introduction. Also, it is better to add the family name (Family Rutaceae) in the introduction.	Thank you for your advice, We have revised it
9	All page	Use the word methanolic extract instead of methanol extract in all the manuscript	Thank you for your advice, We have revised it
10	All page	For the in vivo experiments, it is better to use the word dose instead of the word concentration which is usually used in the in vitro experiments.	Thank you for your advice, We have revised it
11	All page	Please write the scientific name of the plant in italic in all the manuscript including the title	Thank you for your advice, We have revised it
12	All page	Please write the full name of the plant (<i>Zanthoxylum acanthopodium</i>) as full name only in its first appearance in the abstract or introduction then write it as the following <i>Z. acanthopodium</i> .	Thank you for your advice, We have revised it
13	All page	Please use one way of writing the name andaliman. Sometimes the authors write it in capital letter while in other cases, they write it in small letter. Common names of the plants do not need to be capitalized.	Thank you for your advice, We have revised it
14		<p>There are grammar mistakes that need to be corrected such as</p> <p>- Sentence: because they are an inflammatory response product that plays. Correction: because they are inflammatory response products that play.</p> <p>- Sentence: The study's goal was to look at the histological changes in andaliman treatment, as well as the expression of cytokines like IL-10, IL1β, VEGFR1, and TGFβ1 in tissue and serum from cervical cancer rat models.</p> <p>Correction: The study's goal was to look at the effect of andaliman treatment on the histological changes as well as the expression of cytokines like IL-10, IL1β, VEGFR1, and TGFβ1 in tissue and</p>	Thanks for your suggestions, We have sent our manuscript to native speakers. You can find proof of manuscript certificates stating that our paper has been corrected, under the following this table.

		<p>serum from cervical cancer rat models.</p> <p>- Phrase: behind breast cancer. Correction: after breast cancer.</p> <p>- Sentence: family of proteins, which includes Correction: family of proteins including</p> <p>- Sentence: tumor microenvironment cells that stimulates the creation of blood vessels in some cancers. Correction: tumor cells that stimulate the creation of blood vessels in some cancers.</p> <p>- Sentence: Andaliman that have the ability Correction: Andaliman that has the ability</p> <p>- Sentence: expression of cytokines likes Correction: expression of cytokines like</p> <p>- Sentence: cervical cancer model rats had an insignificant weight before treatment. Correction: There was no statistical difference in weight between cervical cancer model and control group before treatment.</p>	
15	Abstract	<p>- Add the word samples after (tissue and serum from cervical cancer rat models).</p> <p>- Delete (for 30 days) that was placed at the beginning of sentence and indicate the route and duration of the administration of the plant extract clearly in the abstract.</p> <p>- Use hematological parameters instead of hematological value.</p> <p>- Avoid using conclusive sentences as facts. Use ZAM increased IL-10 instead of the sentence ZAM also aids IL-10 in inhibiting the proliferation of abnormal cells that continue to differentiate.</p> <p>- The authors need to mention the full name of the abbreviations SOD,</p>	Thank you for your advice, We have revised it


		<p>MDA and NGAL in their first appearance.</p> <ul style="list-style-type: none"> - The authors used TGF1 and TGFβ1 in the abstract. Please identify which one do you want to refer to? 	
16	Introduction	<ul style="list-style-type: none"> - Remove environmental influences as well as - Remove the word viral because cytokines play roles in infections and not only viral infections. - Write the full name of IL-1, HPV, MAPK - Remove (at plasma IL-1 concentrations). - Remove (may all) in the sentence (may all have a role in IL-1β's effects). - Remove (the) from (rejection of the cancer). - Remove differentiated from the sentence (that regulate cell development, maturation, and differentiated differentiation). - Remove italic writing from Vascular endothelial growth factor (VEGF). - Avoid the repetition of writing the full name of VEGF. - Delete (in the histology of cervical cancer tissue) from Andaliman can also alter Mcf-7 Cell Line in the histology of cervical cancer tissue - Change this sentence (So it is hoped that this research on cancer cells will continue and that this plant will be developed into cervical cancer drugs in the future using cytokines therapy) into (it is suggested that this plant can be developed into cervical cancer drugs in the future using cytokines therapy). - Add the word samples after (tissue and serum from cervical cancer rat models) 	Thank you for your advice, We have revised it
17	Materials	<p>Materials</p> <ul style="list-style-type: none"> - Please remove all the dilutions from the section of materials and include it in the methods. The section of materials should include the source of materials only. 	Thank you for your advice, We have revised it

		<ul style="list-style-type: none"> - You should use the past tense in all the methods. For example, were cleaned and not are cleanedetc. - Usually it is written 1.0 percent to 1.5 and not vice versa. - Please identify the route of administration of the extract. - Remove Faculty of Medicine from the sentence (Laboratory of the Faculty of Medicine's Faculty of Medicine). - Change the sentence (The rats are fed standardized rat pellets and provided plenty of water) to (Food pellets and water were provided to the rats). - Change (the rats are formed in an animal model of cancer) to (the rats represent animal models of cancer). - The authors need to identify the number of animals in each group. - Capitalize the word anova and write it as ANOVA. - Capitalize the word Tgfβ1 in (the IL-10 (rat) ELISA kit, the Tgfβ1). 	
18	Results	<ul style="list-style-type: none"> - Correct (p0.05, p=0.040) in all the manuscript. Use < - Change the sentence (The squamous epithelium can tell you if a cell is normal). - Delete the sentence So there was a significant difference between cancer rats and healthy rats. It is a repetition for the previous sentence. - Remove the word cancer from the caption of figure 1 (Effect of ZAM on Cancer Body weight). - Change the following sentence (According to Figure 2, cervix tumors can affect cervical weight in both the control group and the ZAM administration. - There is no need to put marks for the non-significance between groups in the graphs or tables. The authors can talk about the non-significance in the results but not mark them in figures and tables. - It is confusing to write the marks in the figures according to p value. The marks should be written 	Thank you for your advice, We have revised it

		<p>according to the group whereby the comparison was conducted. For instance, you cannot use * and ** for 2 groups that were compared to the same reference group (e.g. C+). You should use a similar mark and write * indicates significance compared to C+.</p> <ul style="list-style-type: none"> - Write the full name of SGOT, SGPT. - Avoid using long sentences such as (In rats, ZAM administration can reduce the expression of IL1β, which promotes the proliferation of cancer cells. In cervical tissue cells, innate immune system cells such as macrophages, Langerhans cells (LC), dendritic cells (DC), neutrophils, Natural Killer (NK) cells, T lymphocytes, and keratinocytes recognize foreign structures not found in the host via receptors such as Toll -like receptors (TLRs) that signal the expression of inflammatory cytokines and chemokines such as interleukin (IL) IL1β, , IL6, IL8, IL12, TNFα and interferon (IFN) -α, -β and -γ). <p>Divide this long sentence.</p>	
19	Discussion	<ul style="list-style-type: none"> - Change this sentence (can increase the volume of the cervix). - In cancer patients, ZAM administration has been shown to protect against benzoapyrene-induced oxidative stress?. Was there a study that was conducted in patients/human by inducing cancer?!. The use of the word patients is misleading. - Write the full name of ROS. - Remove and (and cancer cell spread and metastasis as a genetically unstable entity) 	Thank you for your advice, We have revised it
Reviewer 2			
1	Question 1	The rationale for the study is poorly explained, which makes the manuscript very weak. It has to be strong and properly justified. In the rationale, authors have used MCF-7 cell line to justify the rationale for the study. However, MCF-7 cell line is a breast cancer cell line and the proposed study is about cervical cancer. Please comment on that.	<p>We forgot to report on in vitro studies using heLa cells. We have changed the sentences.</p> <p>Previous studies showed the potency of <i>Z. acanthopodium</i> as an antioxidant, antibacterial against human pathogens, anti-inflammatory, and antiacne. The potency of <i>Z. acanthopodium</i> against breast (MCF-7</p>

			<p>cell line) and cervical cancer cell (HeLa) lines were reported previously.</p> <p>Evaluation of Cytotoxic Activity Alkaloid Fractions of <i>Zanthoxylum acanthopodium</i> DC. Fruits. - Abstract - Europe PMC</p> <p>and</p> <p>Frontiers <i>Zanthoxylum</i> Species: A Review of Traditional Uses, Phytochemistry and Pharmacology in Relation to Cancer, Infectious Diseases and Sickle Cell Anemia Pharmacology (frontiersin.org)</p>
2	Question 2	<p>Authors must have purchased the plant sample from local vendor. However, the certificate of analysis or test confirming the plant species is missing. Please include those tests, which will confirm that the used plant is <i>Zanthoxylum acanthopodium</i>. If possible, this reviewer will suggest to identify the possible molecular substrate of phytochemical responsible for the exerted therapeutic effect.</p>	<p>We have attached a certificate stating that this plant is <i>Zanthoxylum acanthopodium</i>. You can find it under the revision table below!.</p> <p>We used this dose based on a previous study by one of our authors entitled "Acute toxicity test and histological description of organs after giving nano herbal andaliman (<i>Zanthoxylum acanthopodium</i>)" with the results of the toxicity test that andaliman has a low toxic value (LD50 of 9.807g /KgBW ± 0.075). Authors have analyzed the constituents of the plant extract that was used in this study. Andaliman fruit extracts contain various bioactive compounds such as alkaloids, flavonoids, glycosides, saponins, tannins, triterpene/steroids and glycoside anthraquinone. We did not include the phytochemicals responsible for the therapeutic effects given in this manuscript because there are already researchers who have published them. So we just quote it to avoid plagiarism. This study is only limited to histological changes of cervical cells after andaliman administration in vivo.</p> <p>You cant find in this link https://www.smujo.id/biodiv/article/view/6464/4202</p> <p>A review of the bioactivity and flavor properties of the exotic spice “andaliman” (<i>Zanthoxylum acanthopodium</i> DC.): Food</p>

			<p>Reviews International: Vol 35, No 1 (tandfonline.com)</p> <p>and https://iopscience.iop.org/article/10.1088/1755-1315/122/1/012089/pdf</p>
3	Question 3	<p>In the animal model, authors have described that the benzopyrene chemical was injected into the cervix and then after three months of injection, the treatment was provided. Have authors checked the cancer induction before starting the treatment, if yes, then please include the method and discuss the result in the section. Additionally, in general practice the dosage is defined by mg/kg. However, here authors have used dose of 100/200/400mg per animal irrespective of the body weight. Please comment on that. Have authors considered the toxicity profile of the drug and how the dosage was decided. please comment on these. Why authors have not included vehicle treated group in the study as alcohol is used as a vehicle to dissolve the drug, which may have toxic effect if administered through oral route. The route of the dosing is missing. If it is oral, then please comment on the effect of chronic administration of alcohol? How many animals were there in each group?</p>	<p>- . Rats under normal conditions of negative control (C-) were given normal feed and drinking water ad libitum; Groups C+, ZAM100, ZAM200 and ZAM400 were injected into the cervix using 50 mg benzopyrene diluted with corn oil and then left to form a tumour (Sanchala et al., 2018). Tumours in rats were seen after 3 months. Identification of the presence of tumours was carried out using the Pap smear method and cervical dissection of rats by observing preparations with paraffin blocks.</p> <p>We used 50mg of B[a]P for cervical induction, based on a previous study (Sanchala, D., Bhatt, LK, Pethe, P., Shelat, R., & Kulkarni, YA 2018. Anticancer activity of methylene blue via inhibition of heat shock protein 70. <i>Biomedicine & Pharmacotherapy</i>, 107, 1037–1045. doi:10.1016/j.biopha.2018.08.095). However, in the Wistar strain rats, tumours began to appear after 3 months.</p> <p>We used this dose based on a previous study by one of our authors entitled "Acute toxicity test and histological description of organs after giving nano herbal andaliman (<i>Zanthoxylum acanthopodium</i>)" with the results of the toxicity test that andaliman has a low toxic value (LD50 of 9.807g /KgBW ± 0.075). In addition, the use of these doses has been carried out in previous studies, with the results that Andaliman fruit extract in the dose of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW have analgesic effectivity more than 50% compared to mefenamic acid with effectivity. of 93.16%, 89.21%, and 112.01% respectively. Conclusion: Andaliman fruit extract is an effective analgesic.</p>

			<p>We cite the link below (http://ojs.udb.ac.id/index.php/infokes/article/view/1299).</p> <p>We have conducted a pre-study using a control group and a vehicle to examine the effects of chronic alcohol administration. However, there was no significant difference between the control group and the vehicle, so we decided to use only 5 groups in this study. This study used 30 rats and the number of rats in each research group was 6 rats.</p>
4	Question 4	<p>Since the cervical cancer model was developed, the authors are advised to include the visual proof of animal cervical cancer as this will help in concluding the therapeutic effect.</p>	<p>Dear reviewers</p> <p>We cannot display the visual proof in our manuscript, to prevent self-plagiarism, because we have submitted to other journals with the title "macroscopic and microscopic descriptions of cervical tumour in rats after given andaliman" using the photos you requested. And the manuscript has been accepted and is waiting to be published. If we display it in this manuscript, it will cause the data to be published twice. The following is an example of a tumour in the female reproductive organs of rats resulting from benzopyrene injection for 3 months.</p> 
5	Question 5	<p>Additionally, in addition to ELISA, authors are advised to perform other experiments to confirm the validate the molecular changes, this will help in establishing the rigor</p>	<p>Now, We are doing to perform other experiments to confirm the validate the molecular changes, with HeLa cells after being given by andaliman. Please wait for our research with a different title.</p> <p>The study's goal was only to look at the histological changes in andaliman treatment, as well as the expression of cytokines likes IL-10, IL1β, VEGFR1, and TGFβ1 in samples tissue and serum from cervical cancer rat models.</p> <p>This research is only as basic research to continue further research</p>
Minor concern			

1	Title	The title is not clear, which needs to be updated	We have updated our title from “ The Cytokines Expression on Histological Changes of Cervical Cancer by Andaliman (<i>Zanthoxylum acanthopodium</i> DC)” To “ Histological changes of cervical tumours following <i>Zanthoxylum acanthopodium</i> DC treatment, and its impact on cytokine expression”
2	Abstract	The manuscript has many redundancies, which needs to be eliminated. Such as line 2 and 3, and line 3 and 4 in abstract. Please review entire manuscript and eliminate it. Please update the entire abstract. An abstract should give overview of entire manuscript.	Thank you for your advice, We have revised it
3	All page	The manuscript is very poorly written with many grammatical errors and few incomplete sentences. The authors are advised to take help from writing service and update the manuscript before submitting again. Keep the same font and spacing throughout the manuscript.	Thanks for your suggestions, We have sent our manuscript to native speakers. You can find proof of manuscript certificates stating that our paper has been corrected, under the following this table.
4	Results	The manuscript does not describe the data representation, such as Mean +- SD or Mean +- SEM. Additionally, check the "p" values in entire manuscript. Some of the places it does not match with the description.	Thank you for your advice, We have revised it
5	Abbreviation	Abbreviation section is missing.	Thank you for your advice, We have revised it. We have added after references
6	Method section	A method should contain all the required details. In the entire manuscript, it has been neglected, please update the entire method section. The materials section is poorly written. In the section 2.6, which tissue was used for analysis, which method was used to analyze and how the analysis was done. Similar comments are applicable to 2.7.	Thank you for your advice, We have revised it
7	Results	First paragraph in section 3.4 does not make any sense. Please review the data and update it.	Thank you for your advice, We have revised it
8	Legends	Figure legends and table titles are poorly written.	Thank you for your advice, We have revised it
9	Figures	Keep the coloring schemes for the figures constant.	Thank you for your advice, We have revised it

10	Figures	Some of the figures are of poor quality.	Thank you for your advice, We have revised it
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