

Dear Editor of the International Journal of Technology,

Herewith we submit "Fifth Revision" of our research article entitled: "Effect of Cinnamaldehyde on the Surface Characteristics of POP-CaCO<sub>3</sub> Hydrogel for Biomedical Purposes" that we submit solely for the International Journal of Technology for ISBE Special Edition.

We have changed the title into: Effect of Cinnamaldehyde as an Anti-inflammatory Agent on the Surface Characteristics of POP-CaCO<sub>3</sub> Hydrogel for Bone Substituting Purposes in Biomedicine.

We also have revised the manuscript as referred to reviewers' comments. Additional data have also been added to the manuscript. The detailed revision has been listed in the following consolidated comments. The highlighted version is also attached and submitted accordingly.

There are 4 files we submitted:

1. The revised manuscript (in Doc and PDF)
2. The revised manuscript – Highlighted
3. The consolidated comments or response to review in detailed
4. The previous uploaded documents for previous revisions

We believe that the article will contribute significantly in the development of biomedical technology through publication in the International Journal of Technology.

Thank you and we hope to hear good news about our article.

Best wishes,

Ika Dewi Ana, corresponding author

## List of Changes

Manuscript:

### Effect of Cinnamaldehyde as an Anti- inflammatory Agent on the Surface Characteristics of POP-CaCO<sub>3</sub> Hydrogel for Bone Substituting Purposes in Biomedicine

Response and Revision made by Author(s)

Reviewer #1:

| No | Comments   | Revision/Changes  |
|----|--|---|
| 1. | <b>Introduction:</b><br>Authors must answer and response for each reviewer's comment and highlight in different colour.                                    | In the previous revision (October 8, 2020), we have already response (using template) all reviewer's comments in detail, revised the manuscript, and highlighted the revision in yellow colors. All the documents have been submitted accordingly.<br>We resubmit all the documents, along with this second consolidated comment for reviewers. |
| 2. | <b>Methodology:</b><br>Authors must answer and response for each reviewer's comment and highlight in different colour.                                     | In the previous revision (October 8, 2020), we have already response (using template) all reviewer's comments in detail, revised the manuscript, and highlighted the revision in yellow colors. All the documents have been submitted accordingly.<br>We resubmit all the documents, along with this second consolidated comment for reviewers. |
| 3  | <b>Results and Discussion:</b><br>Authors must answer and response for each reviewer's comment and highlight in different colour.                          | In the previous revision (October 8, 2020), we have already response (using template) all reviewer's comments in detail, revised the manuscript, and highlighted the revision in yellow colors. All the documents have been submitted accordingly.<br>We resubmit all the documents, along with this second consolidated comment for reviewers. |
| 4  | Figure 2 and 6 are not clear. Please provide high resolution and/or make it larger. In Figure 2, the figure contact angle makes it in bigger or remove it. | We have already revised Figure 2 to make it larger in better resolution.<br>We also have changed Figure 6 (Now it is Figure 7) with a newly taken micrograph pictures with scale bar.   |
| 5  | In Figure 3, it should be FTIR spectra.  | The Figure 3 and explanation have been revised accordingly.   |
| 6  | Why in FTIR spectrum of Gelatin the peak at 2000 - 2500 cm <sup>-1</sup> goes to up? Any correction?   | The peak at 2000-2500 cm <sup>-1</sup> shows higher vibration intensity because the spectra only contained gelatin without any additional materials. In a single composition, the intensity of the vibration is usually higher compared to a material composed of a mixture >1 material.  |

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| 7  | Figure 3. The product is not clear in the functional groups.   | We insert the complete reaction synthesis that may occur between gelatin, CaCO <sub>3</sub> , and cinnamaldehyde.  |
| 8  | Why for double bond is not similar length?   | We have already revised it as in Figure 4.   |
| 9  | Information scale and other information in Figure 6 is not clear.  | We have already revised it with higher magnification scales and put appropriate scale bar accordingly.   |
| 10 | It is interesting discussion for hydrophilicity due to the contact angle and surface roughness. If author can add other data for comparison in Table. It is much better. | Table 2 has already contained the comparison on contact angle and surface roughness. However, we inserted Figure 8 to clarify the results of the study.  |
| 11 | <b>References:</b><br>Authors must answer and response for each reviewer's comment and highlight in different color.   | In the previous revision (October 8, 2020), we have already response (using template) all reviewer's comments in detail, revised the manuscript, and highlighted the revision in yellow colors. All the documents have been submitted accordingly.<br>We resubmit all the documents, along with this second consolidated comment for reviewers.<br><br>Furthermore, previously we have already added 3 IJTech relevant journal, put also other references used in discussion, as well as revised the references.<br><br>One journal is in Bahasa Indonesia, national accredited. The journal is very relevant. |
| 12 | <b>Title</b>   | Title has already changed from:<br><br>Effect of Cinnamaldehyde on the Surface Characteristics of POP-CaCO <sub>3</sub> Hydrogel for Biomedical Purposes (Original)<br><br>Into Effect of Cinnamaldehyde as an Anti-inflammatory Agent on the Surface Characteristics of POP-CaCO <sub>3</sub> Hydrogel for Bone Substituting Purposes (08/10/2020)<br><br>Effect of Cinnamaldehyde on the Surface Characteristics of POP-CaCO <sub>3</sub> Hydrogel for Bone Substituting Purposes in Biomedicine (21/10/2020).   |

*Response and Revision made by Author(s)*

**Reviewer #2:**

**Thank you for the review.**

## Attachment 1. Sent on October 8, 2020

### List of Changes

Manuscript:

#### Effect of Cinnamaldehyde on the Surface Characteristics of POP-CaCO<sub>3</sub> Hydrogel for Biomedical Purposes

Response and Revision made by Author(s)

Reviewer #1:

| No | Comments  | Revision/Changes   |
|----|---|--|
| 1  | Please revise according to the reviewer's comment and it is suggested to include at least 3 relevant IJTech articles as references. | The comprehensive revision has been done. There are 4 relevant IJTech articles are added in the references.  |
| 2  | Authors must explain what has been done.  | Previous studies have been explained to comprehensively describe what has been done.   |
| 3  | Authors must add any variables for experimental or others, please introduce in introduction!  | All variables related to surface topography have been added and presented in this article (SEM micrograph, contact angle to measure hydrophilicity or wettability, and surface roughness). The three variables are the ones needed to provide prior data for in vitro cells and in vivo animal studies.  |
| 4  | What authors expected from these results?   | By the incorporation of cinnamaldehyde into the hydrogel, it was expected that POP-hydrogel CaCO <sub>3</sub> composite will have anti-inflammatory capability. However, since cinnamaldehyde have both lipophilic and hydrophilic sides, cinnamaldehyde can affect the mechanical and surface properties, especially surface properties, of the composite when they were mixed. Moreover, surface properties, especially surface chemistry, hydrophilicity, and surface topography, influence the interaction between cells and substrate to the environment surrounding the material. Since the success of the implant depends on the materials surface ad cells interaction, thus the data on surface characteristics are significant to be investigated. These have been inserted in the revision. |

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| 5  | Author must mention and clarify the position results. What is the new from this study?                                 | The incorporation of hydrogel CaCO <sub>3</sub> into POP is known to be an originality of the study, to solve fast degradability of POP. None of the literatures except from our group has been published. Moreover, the cinnamaldehyde loaded into hydrogel CaCO <sub>3</sub> is the novelty of the gelatin-ceramics hydrogel development done in the area of biomedicine and materials in medicine in general. |
| 6  | Authors must add the objective of this study in the Introduction.  | The objective of this study has been provided in the introduction.   |
| 7  | Add more information for the sources used.   | Revision has been made accordingly in the method section.  |
| 8  | Combine to be one for Table 1 and 2.   | This has been revised accordingly.   |
| 9  | Add more discussion for FTIR and SEM-EDX. Author can compare with the previously study and or same starting materials. | We have added the SEM picture of the hydrogel without POP as comparison.   |
| 10 | Remove or combine Tables 2 and 3. Just discuss this data and compare with others.                                      | Table 2 and 3 have been combined.  |
| 11 | Follow the Harvard System Reference in bahasa, please translate it.  | Checking and revision have been done accordingly.  |

**Reviewer #2:**

| <b>No</b> | <b>Comments</b>   | <b>Revision/ Changes</b>   |
|-----------|---|--|
| 1         | Revise the abstract and conclusion. In abstract: - Reduce the state of the art and/or hypothesis. It is too long "Tissue engineering offers . . . low water solubility" - Add the significant results and add the recommendation. | Abstract and conclusion have been revised based on the suggestion of Reviewer #1 and #2  |
| 2         | Conclusion: add future work.  | Future works have been inserted into the conclusion. Conclusion has been revised accordingly.  |
| 3         | Font follow the guide of authors.   | This has been revised accordingly.   |
| 4         | Revise the title.   | The title has been changed into more specific one.<br>Previous title:<br><u>Effect of Cinnamaldehyde on the Surface Characteristics of POP-CaCO<sub>3</sub> Hydrogel for Biomedical Purposes</u><br>Revised title:<br><u>Effect of Cinnamaldehyde as an Anti-inflammatory Agent on the Surface Characteristics of POP-CaCO<sub>3</sub> Hydrogel for Bone Substituting Purposes</u> |