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**Judul Artikel** : Revealing Novel Source of Breast Cancer Inhibitors from Seagrass *Enhalus acoroides*:  
In Silico and In Vitro Studies

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The screenshot shows a Gmail inbox with a selected email. The email is from Molecules Editorial Office (molecules@mdpi.com) to the user, dated Sunday, February 11, 2024, at 20:39. The subject is "[Molecules] Manuscript ID: molecules-2891177 - Co-Authorship Confirmation".

The email body contains the following text:

Dear Professor Prajoko,

We are writing to let you know that we have received the below submission to Molecules for which you are listed as a co-author.

Manuscript ID: molecules-2891177  
Type of manuscript: Article  
Title: Revealing novel source of breast cancer inhibitors from seagrass  
Enhalus acoroides: In Silico and In Vitro studies  
Authors: Yan Wisnu Prajoko \*, Faqizal Ria Qhabibi, Timothy Sahala Gerardo, Kanandya Kizzandy, Krisanto Tanjaya, Sebastian Emmanuel Willyanto, Happy Kurnia Permatasari, Reggie Surya, Nelly Mayulu, Nurpudji Astuti Taslim, Raymond Rubianto Tjandrawinata, Rony Abdi Syahputra, Trina Ekawati Tallei, Apollinaire Tsopmo, Bonglee Kim, Rudy Kurniawan, Fahrul Nurkolis  
Received: 10 Feb 2024

In order to confirm your connection to this submission, please click here to confirm your co-authorship:  
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Kind regards,  
Molecules Editorial Office

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**Journal** *Molecules* (ISSN 1420-3049)

**Manuscript ID** molecules-2891177

**Type** Article

**Title** Revealing novel source of breast cancer inhibitors from seagrass *Enhalus acoroides*: In Silico and In Vitro studies

**Authors** Yan Wisnu Prajoko \*, Faqrizal Ria Qhabibi, Timothy Sahala Gerardo, Kanandya Kizzandy, Krisanto Tanjaya, Sebastian Emmanuel Willyanto, Happy Kurnia Permatasari, Reggie Surya, Nelly Mayulu, Nurpudji Astuti Taslim, Raymond Rubianto Tjandrawinata, Rony Abdi Syahputra, Trina Ekawati Tallei, Apollinaire Tsopmo, Bonglee Kim, Rudy Kurniawan, Fahrul Nurkolis

**Special Issue** Marine Bioactives for Human Health

**Abstract** *Enhalus arcoides* is a highly beneficial type of seagrass. Prior studies have presented proof of the bioactivity of *E. acoroides*, suggesting its potential to combat cancer. Therefore, this study aims to delve deeper into *E. acoroides* bioactive molecules profile and their direct biological anticancer activities potentials through the combination of in-silico and in-vitro studies. This study conducted metabolite profile analysis on *E. acoroides* utilizing HPLC-ESI-HRMS/MS analysis. Two extraction techniques, ethanol, and hexane, were employed for the extraction process. Furthermore, the in-silico study was conducted using molecular docking simulations on the HER2, EGFR tyrosine kinase and HIF-1 $\alpha$  protein receptor. Afterward, the antioxidant activity of *E. acoroides* metabolites was examined to ABTS, and the antiproliferative activity was tested using an MTT assay. An in-silico study revealing its ability to combat breast cancer by inhibiting HER2/EGFR/HIF-1 $\alpha$  pathway through molecular docking. In addition, the MTT assay demonstrated that higher dosages of metabolites from *E. acoroides* increased the effectiveness of toxicity against cancer cell lines. Additionally, the study demonstrated that the metabolites possess the ability to function as potent antioxidants, effectively inhibiting a series of carcinogenic mechanisms. Eventually, this study showed a new approach to unveiling the *E. acoroides* metabolites' anticancer activity through inhibiting HER2/EGFR/HIF-1 $\alpha$  receptors, great cytotoxicity, and a potent antioxidant property to prevent a carcinogenic cascade.

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Authors' Responses to Reviewer's Comments (Reviewer 1)

**Author's Notes** **Reviewer 1 Comments:**

The present work is based on the potential of *Enhalus acoroides* extracts as anticancer agents. I consider the work to be very comprehensive, well-written, and justified.

**Thank you for your valuable comments and appreciation, it's highly appreciated!**

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Authors' Responses to Reviewer's Comments (Reviewer 1)

**Author's Notes** **Reviewer 1 Comments:**

The present work is based on the potential of *Enhalus acoroides* extracts as anticancer agents. I consider the work to be very comprehensive, well-written, and justified.

**Thank you for your valuable comments and appreciation, it's highly appreciated!**

Some minor observations:

1. In the materials and methods section, the methodology should be detailed a bit more, for example, in the case of the study of HIF-1 $\alpha$ , EGFR tyrosine kinase, and HER2 expressions, it explains the detection procedure but does not explain the sample preparation.

**Response:**

# Thank you for your constructive input on our manuscript. We appreciate your input. We have revised this part this accordingly.

2. Regarding the statistical analysis, the authors mostly conducted pairwise studies according to the figure, but they should have performed a global ANOVA since the results may vary in that case.

**Response:**

# Thank you for your constructive input on our manuscript. We appreciate your input. We have revised this part this accordingly, we have added the new description of the global ANOVA analysis as per your suggestion.

3. Finally, the in silico studies are with pure compounds (which is logical) while the in vitro assays are with complete extracts. Did the authors consider including at least some pure standards? Although not all compounds are commercially available, some of them are quite common and accessible.

**Response:**

# We have added the in vitro study data of LD50 anticancer regarding two single commercial compounds Luteolin (C2) and Thalassiolin C (C8) to this part accordingly. Thank you for your constructive input on our manuscript.

Review Report Form

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### Review Report Form

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 English very difficult to understand/incomprehensible  
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Does the introduction provide sufficient background and include all relevant references?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Are the conclusions supported by the results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments and Suggestions for Authors The present work is based on the potential of *Enhalus acoroides* extracts as anticancer agents. I consider the work to be very comprehensive, well-written, and justified. Some minor observations: In the materials and methods section, the methodology should be detailed a bit more, for example, in the case of the study of HIF-1 $\alpha$ , EGFR tyrosine kinase, and HER2 expressions, it explains the detection procedure but does not explain the sample preparation. Regarding the statistical analysis, the authors mostly conducted pairwise studies according to the figure, but they should have performed a global ANOVA since the results may vary in that case. Finally, the *in silico* studies are with pure compounds (which is logical) while the *in vitro* assays are with complete extracts. Did the authors consider including at least some pure standards? Although not all compounds are commercially available, some of them are quite common and accessible.

Submission Date 10 February 2024  
Date of this review 19 Feb 2024 16:19:52

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Authors' Responses to Reviewer's Comments (Reviewer 2)

Author's Notes **Reviewer 2 Comments:**

This study investigated the metabolites from seagrass *E. acoroides* and their potential anticancer activity to combat breast cancer through molecular docking and MTT assay. Several problems need to be addressed as follows.

1. The manuscript needs to be carefully proofread.

**Response:**

# We have proofread this manuscript carefully and accordingly. Thank you for your constructive input on our manuscript, it's much appreciated.

2. What is the percentage of each compound in the extracted metabolites? How does it correlate to anticancer activity?

**Response:**

# The percentage of each compound cannot be observed because this is a qualitative study using HPLC-ESI-HRMS/MS analysis. This study is to observe compounds qualitatively and because some compounds are new, reagents for quantitative analysis are not yet available and this is a limitation of this research. However, we have added the in vitro study data of LD50 anticancer regarding two single commercial compounds Luteolin (C2) and Thalassiolin C (C8) to this part accordingly as per your suggestion and reviewer 1 suggestion to make it correlate with their anticancer activity. Thank you for your constructive input on our manuscript.

3. In Table 6, the unit for LD50 values needs to be added.

**Response:**

Thank you and We have revised this part this accordingly.

4. In Figure 3, it would be good to label the statistical differences among different samples concisely.

**Response:**

# Thank you for your constructive input on our manuscript. We appreciate your input. We have tried to make this figure label more concisely, we have filtering the label only with  $p < 0.0001$ .

Thank you for your constructive comments, they are highly appreciated. We have revised extensively and thoroughly according to the reviewer comments, the manuscript with highlights is submitted.

# Thank you for your constructive input on our manuscript. We appreciate your input. We have tried to make this figure label more concisely, we have filtering the label only with  $p < 0.0001$ .

Thank you for your constructive comments, they are highly appreciated. We have revised extensively and thoroughly according to the reviewer comments, the manuscript with highlights re-submitted.

### Review Report Form

Quality of English Language

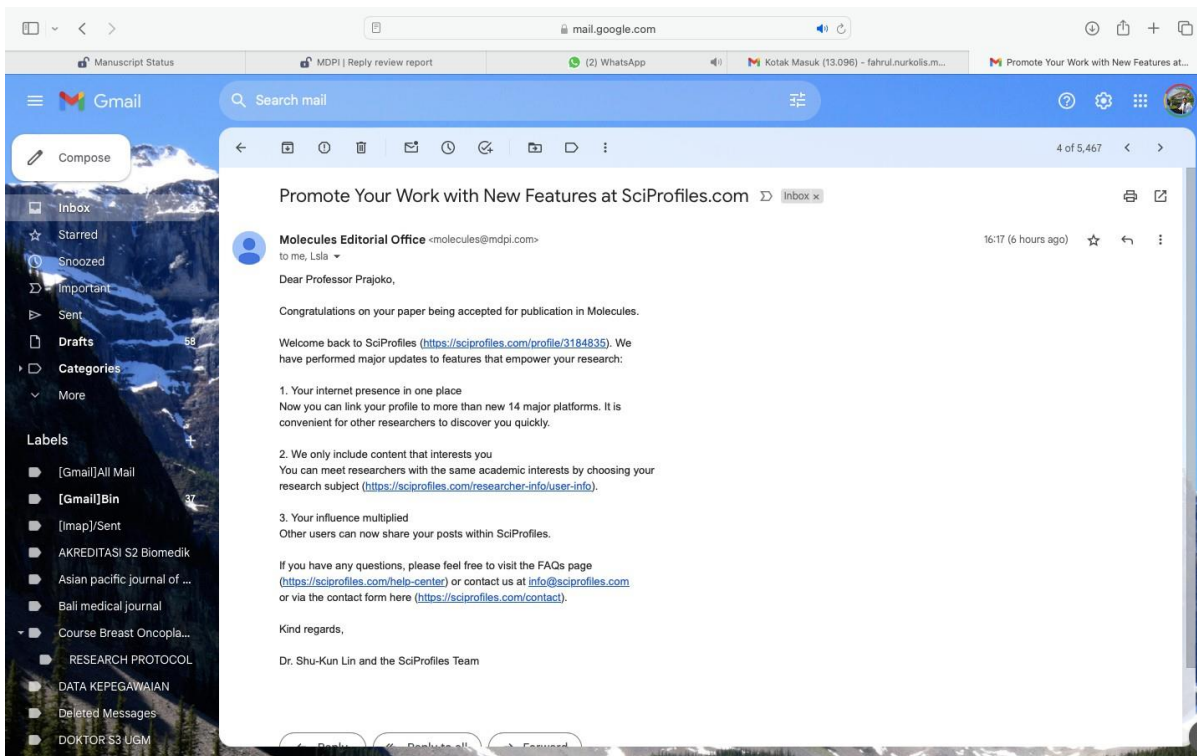
- I am not qualified to assess the quality of English in this paper
- English very difficult to understand/incomprehensible
- Extensive editing of English language required
- Moderate editing of English language required
- Minor editing of English language required
- English language fine. No issues detected


	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Are the conclusions supported by the results?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments and Suggestions for Authors

This study investigated the metabolites from seagrass *E. acoroides* and their potential anticancer activity to combat breast cancer through molecular docking and MTT assay. Several problems need to be addressed as follows.

- The manuscript needs to be carefully proofread.
- What is the percentage of each compound in the extracted metabolites? How does it correlate to anticancer activity?






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## Revealing Novel Source of Breast Cancer Inhibitors from Seagrass *Enhalus acoroides*: In Silico and In Vitro Studies

by Yan Wisnu Prajoko <sup>1,\*</sup>, Faqizal Ria Qhabibi <sup>2</sup>, Timothy Sahala Gerardo <sup>2</sup>, Kanandya Kizzandy <sup>2</sup>, Krisanto Tanjaya <sup>2</sup>, Sebastian Emmanuel Willyanto <sup>2</sup>, Happy Kurnia Permatasari <sup>2</sup>, Reggie Surya <sup>3</sup>, Nelly Mayulu <sup>4</sup>, Nurpudji Astuti Taslim <sup>5</sup>, Raymond Rubianto Tjandrawinata <sup>6</sup>, Rony Abdi Syahputra <sup>7</sup>, Trina Ekawati Taliei <sup>8</sup>, Apollinaire Tsopmo <sup>9</sup>, Bonglee Kim <sup>10,11</sup>, Rudy Kurniawan <sup>12</sup> and Fahrul Nurkolis <sup>12</sup>

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