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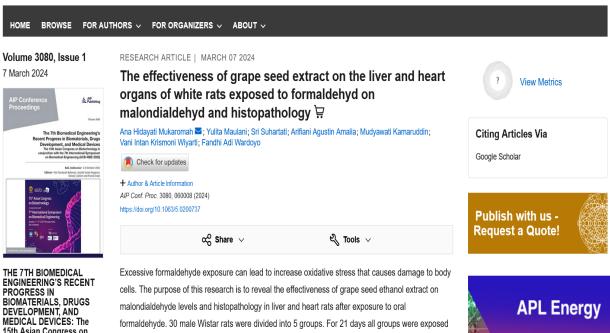
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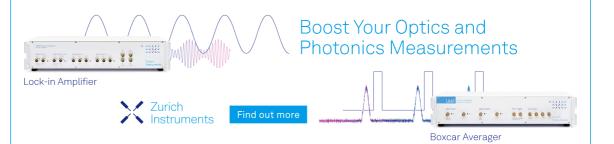
The effectiveness of grape seed extract on the liver and heart organs of white rats exposed to formaldehyd on malondialdehyd and histopathology

Ana Hidayati Mukaromah ➡; Yulita Maulani; Sri Suhartati; Arifiani Agustin Amalia; Mudyawati Kamaruddin; Vani Intan Krismoni Wiyarti; Fandhi Adi Wardoyo

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The Effectiveness of Grape Seed Extract on The Liver and Heart Organs of White Rats Exposed to Formaldehyd on Malondialdehyd and Histopathology

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Abstract. Excessive formaldehyde exposure can lead to increase oxidative stress that causes damage to body cells. The purpose of this research is to reveal the effectiveness of grape seed ethanol extract on malondialdehyde levels and histopathology in liver and heart rats after exposure to oral formaldehyde. 30 male Wistar rats were divided into 5 groups. For 21 days all groups were exposed to 5mg/200g formaldehyde except the negative control group. Three treatment groups received ethanolic extracts of grape seeds at doses of 35, 70, and 140mg/200g BWrats/day, respectively. The results showed that the administration of EBA can improve the liver exposed to oral formaldehyde. MDA levels, an indication of oxidative stress, have decreased, and liver histopathology has improved according to *manja roenigk* scoring. EBA treatment had no direct impact on the MDA levels and recovery of heart organs that had been exposed to oral formaldehyde.

Keywords: Grape seed ethanol extract, liver, heart

INTRODUCTION

The unrestricted use of the dangerous chemical formaldehyde as a food additive is prohibited. Formaldehyde can be ingested by people orally through food preservatives, inhalation, or direct skin contact. According to the International Program on Chemical Safety (IPCS), the maximum amount of formaldehyde that the body may tolerate is 0.1 mg/L in drinking water or 0.2 mg in ingestion. Malondialdehyde, the byproduct of the lipid peroxidation chain reaction, is a sign of oxidative stress. Giving exogenous antioxidants can lower the rise in MDA levels, which are directly inversely proportional to the rise in free radicals [1,2,3].

One of the fruit plants that has a significant amount of resveratrol and other polyphenolic compounds that are active in a number of bodily metabolisms is red wine (Vitis vinifera). Because grape seed extract contains a variety of phenolic compounds, between 60 and 70 percent of the polyphenols from grapes are found in the seeds. The effectiveness of grape seed extract has been the subject of numerous investigations. The harmful effects of methionine on the heart, liver, and kidneys of laboratory rats can be lessened by grape seed extract. Rats exposed to cigarette smoke can drastically lower their MDA levels by taking grape seed extract. With a dose of 100-500 mg / 175 gBB of grape skin extract, plasma MDA levels in rats on a high cholesterol diet were likewise lowered [4,5,6].

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MATERIALS AND METHODS

Upon ethical approval no 659/KEPK-FKM/UNIMUS/2022, the research was carried out in the University of Muhammadiyah Semarang's laboratory. The population consisted of male true rats (*Rattus novergicus*) of the wistar strain that were collected from the University of Muhammadiyah Semarang's experimental animal laboratory.

In this study, different dosages of grape seed ethanol extract—35, 70, and 140 mg/BW rats/day were employed in each group. For 21 days, three groups (P1; P2; P3) were given grape seed extract at doses of 35; 70; and 140 mg/BW rat/day, respectively, with the exception of the negative control group. Oral formaldehyde was administered to all groups except the negative control group at a rate of 5mg/BW rats/day.

Preparation of the Extract of Grape Seeds

Grape seeds were cleaned, collected in a glass container, and dried for two days in an oven at 50°C. The dried grape seeds were mixed, put through a 60-mesh filter, and then put through another 100-mesh sieve. The obtained grape seed powder was weighed (47g) and macerated for 24 hours a day for 3 days in 96% ethanol in a volume that was three times the volume of the powder. In order to eliminate ethanol, the collected filtrate evaporated at 45°C. After that, place in a water bath heated to 45°C until the liquid becomes thick. Various concentrations of grape seed ethanol extract—35, 70, and 140 mg/BW rat/day—were produced [3].

Design in group

In plastic cages, the animals were arbitrarily split into five groups. There were five rats per enclosure, and they were handled as follows.

- 1- Five rats in the negative control group were fed normally.
- 2- Positive control group: consists of 5 rats treated orally with formaldehyde 5mg/BW rat for 21 days
- 3- In the First Group, there were five rats that were given 35mg/BW of grape seed extract and 5mg/BW of formaldehyde for 21 days.
- 4- The Second Group was comprised of five rats that were given 70mg/BW of grape seed extract and 5mg/BW of formaldehyde for 21 days.
- 5- The Third Group was made up of five rats that were given 140mg/BW of grape seed extract and 5mg/BW of formaldehyde for 21 days.

Kill the Animals

After getting treated for 21 days, the entire group was put to death on day 22 by having the liver and heart removed during surgery and administered an anesthetic through inhalation. The organs were then washed with physiological NaCl, placed in PBS 1x solution to measure MDA levels, and placed in 10% Neutral Buffered Formalin (NBF) fluid at a ratio of 1:10 [5,7]

Measurement of MDA and Tissue Section

The liver and heart supernatants were pipetted up to 400 ml, 1 ml of distilled water, 200 ml of 10% TCA, 200 ml of 1% TBA, and 200 ml of 1N HCl were added, and the mixture was then homogenized in a centrifuge at 3000 rpm for 10 minutes. For 10 minutes, the mixture was heated in a water bath at 95°C. The mixture was heated and subsequently chilled to room temperature. The mixture was then put into a cuvette and filtered using filter paper before the sample's absorbance was measured with a UV spectrophotometer.

The liver and heart were cut lengthwise, each organ was fixed for at least 24 hours in 10% NBF, and the histopathology tissue was processed using a tissue processor The following procedures were carried out [8]: a-Dehydration; b- Cleaning; c- Infiltration; d- Embedding; e- Sectioning; f- Staining; and g- Mounting.

RESULTS AND DISCUSSIONS

An earlier technique to identify the presence of particular chemical components was phytochemical analysis, which was performed on the ethanol extract of red grape seeds (*Vitis vinifera*). The analysis revealed that triterpenoids, phenolic compounds, flavonoids, and tannins were present in the ethanolic extract of grape seeds [9].

The mean measurements were obtained as follows the MDA levels in each treatment group were read for absorbance:

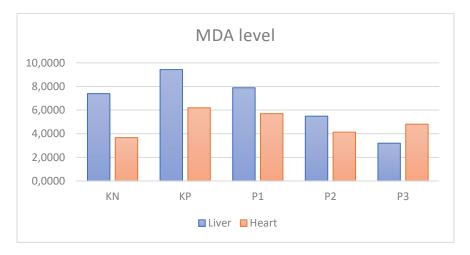


FIGURE 1. White rats' livers and hearts had reduced MDA levels.

Based on Fig 1, it was determined that the data passed the Shapiro-Wilk data normality test with a p-value of > 0.05, indicating that they are normally distributed. With a result of 0.141 in the homogeneity test, it was determined that the data was homogeneous. Additionally, a test utilizing the one-way ANOVA method was conducted, and a result of 0.024 indicated that there was a relationship between variations in the negative control group, the positive control group, treatment 1, treatment 2, and treatment 3 on MDA levels in the liver organ. The post hoc test that produced a sig result was used to continue processing the data. The KP group has a value of 0.021 in comparison to P3, which indicates that there is a substantial difference between the two groups.

The Shapiro Wilk data normality test revealed a p-value > 0.05, indicating that the data are normally distributed. The homogeneity test result was 0.761, which led to the conclusion that the data was homogeneous. The results of the one-way ANOVA test showed a value of 0.803 > 0.05, indicating that there was no interaction between the MDA levels in the heart organ and variations in the negative control group, the positive control, treatment 1, treatment 2, or treatment 3.

After being exposed to oral formaldehyde at a rate of 5 mg/BW rat/day, the positive control group saw an increase in liver MDA levels in contrast to the negative control group (Table 7). Histopathological evaluations of the livers in the positive control group received lower scores than those in the negative control group (Table 11), suggesting that the livers in the positive control group were of lower quality. MDA levels rise in rats who are given sublingual formaldehyde. MDA, a result of the lipid peroxidation chain reaction, is a gauge of oxidative stress. MDA levels increase as a consequence of oxidative stress, which increases the body's free radical levels [2].

Reactive oxygen species (ROS) are among the most prevalent free radicals in the body's biological system (ROS). Exogenous ROS are typically created when the body is exposed to substances or radicals from the outside, in this case the deadly toxin formaldehyde. Superoxide ($^{*}O_{2}$), hydroxyl ($^{*}OH$), peroxyl (ROO), hydrogen peroxide ($^{H}_{2}O_{2}$), singlet oxygen ($^{1}O_{2}$), nitric oxide (NO), peroxynitrite (ONOO), and hypochlorous acid are the components of reactive oxygen (HOCl). Superoxide is the most prevalent free radical that the body produces. It will become hydrogen peroxide from this superoxide ($^{H}_{2}O_{2}$). In the propagation stage, this hydrogen will be transformed into hydroxyl radicals ($^{*}OH$). These hydroxyl radicals disrupt cell structure and impair cell function by causing lipid peroxidation in cell membranes. Through a process known as lipid peroxidation, MDA is created. This process starts when a hydroxyl radical group (OH) removes a hydrogen atom (H) from a PUFA molecule, which is a crucial part of the phospholipids that make up cell membranes. Peroxyl radicals (ROO) are created when these lipid radicals combine with oxygen (O2) to create MDA [10,11].

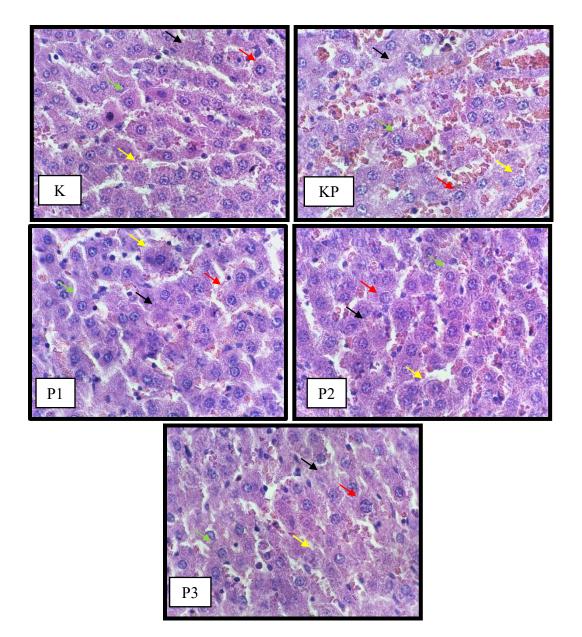


FIGURE 2. Rat liver histopathological preparations. Necrosis (black arrow), parenchymatous (yellow arrow), and hydrops are indications of cell injury (red arrow). Green arrows indicate normal tissue. Magnification 400x and HE painting.

Liver observation consisted of 100 cells spread over 4 fields of vision. The quantity of each type of cell—necrosis, deg. hydropic, deg. parenchymatous, and normal—found was multiplied by the multiplier factor (score:1/2/3/4) to determine the total amount of cells. Gathered, averaged, and an SPSS test was run.

Processed result with an average Shapiro-Wilk normality test p-value > 0.05, indicating a regularly distributed. The result was determined to be homogeneous (p>0.05) after a value of 0.056 was achieved in the homogeneity test. Afterward, the one-way ANOVA test was performed, and a result of 0.000 0.05 was obtained, indicating that there is a relationship between variations in the negative control group, the positive control group, treatments 1, 2, and 3 and MDA levels. The post hoc test that produced a sig result was used to continue processing the data. The results of the KN group with KP, P2 group with KP, and P3 group with KP are 0.05, whereas the P1 group with KP values are >0.05. According to these findings, each group had significant variations, with the exception of the P1 group that had KP.

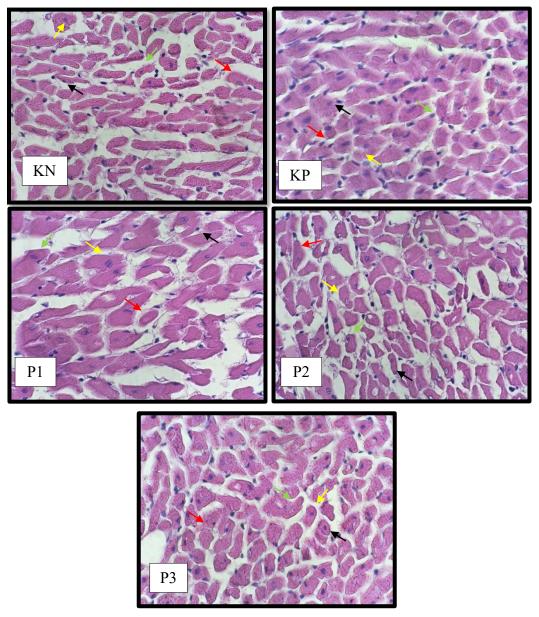


FIGURE 3. Rat heart histopathological preparations. Pyknosis (black arrow), karyorrhexis (yellow arrow), and karyolysis are indications of cell injury (red arrow). Green arrows indicate healthy cells. Magnification 400x and HE painting.

The percentage of normal heart cells was determined using the formula based on observations of the heart organs from each field of view, and a normalcy test was then carried out. The Shapiro Wilk normality test was found to have a p-value > 0.05, indicating that the data was normally distributed. The homogeneity test result was 0.127, which led to the conclusion that the results were homogeneous (p>0.05). Then, using a one-way ANOVA test, it was determined that there was no significant difference in the alterations in normal rat heart muscle cells between the negative control group, the positive control, treatments 1, 2, and 3. The p value for this test was 0.370.

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The results of this study revealed that red grape seed extract treatment had a substantial impact on lowering MDA levels and enhancing cell structure in the livers of rats given oral formaldehyde. This is consistent with Oktaviananda's research from 2017 on how administering grape seed extract (*Vittis vinifera*) to white wistar rats exposed to cigarette smoke affected MDA levels and bronchial histology. The optimal dosage of grape seed extract administered to laboratory animals exposed to cigarette smoke was 5.4mg/rat [3].

According to research by Ahmed et al (2020), 50g/1L grape seed water extract can lessen methionine's harmful effects on the liver, kidneys, and hearts of experimental mice as determined by enzyme tests (LDH, CK, SGOT, and SGPT) and histology [5]. Another study found that raising GSH (glutathione decreased), T-AOC (antioxidative capabilities), decreasing plasma MDA, and improving skeletal muscle in rats reduced weariness brought on by excessive activity (exercise) [12].

The results of MDA levels and organ histological observations in the heart organ indicated that there was no significant effect of grape seed extract on oral formaldehyde exposure in any of the treatment groups. These findings were made possible by the fact that neither the therapeutic dose of grape seed extract nor the dose of formaldehyde exposure had an immediate impact on the heart. The circulatory system pumps blood from the lungs into the heart, where it is subsequently distributed throughout the body. In contrast to the liver's primary role as a toxin detoxifier [13]. Another explanation is that the reason for lower MDA levels and inferior heart organ healing is a brief exposure time of only 21 days. According to Perez et al. (2019), blood samples used to measure CKMB, TG, or HDL characteristics frequently show the impact of grape seed extract for cardiovascular therapy [14].

According to Serrano et al's (2018) research on grape seed or skin extract for cardiovascular risk, the timing of the medication has a significant impact on therapeutic efficacy. Grape seed or skin extract administered chronically for 3-12 weeks or occasionally at higher doses of 500mg/kgBW/day did not significantly alter platelet, triglyceride, or HDL levels at high doses (100-345mg/BW) [15].

CONCLUSION

The conclusion of this research backs up the idea that white rats given oral formaldehyde at a dose of 5mg/BW had affected MDA levels and liver histology. However, formaldehyde 5mg/BW rats had no impact on MDA concentrations or histology in rat heart. The treatment of grape seed extract could decrease MDA levels and the histopathological condition of the liver in white rats exposed to the highest formaldehyde exposure dose—14 mg/BW rat. Treatment of grape seed extract can decrease MDA and improve histopathology in the heart organs of white rats exposed to formaldehyde, even though the improvement was not significant.

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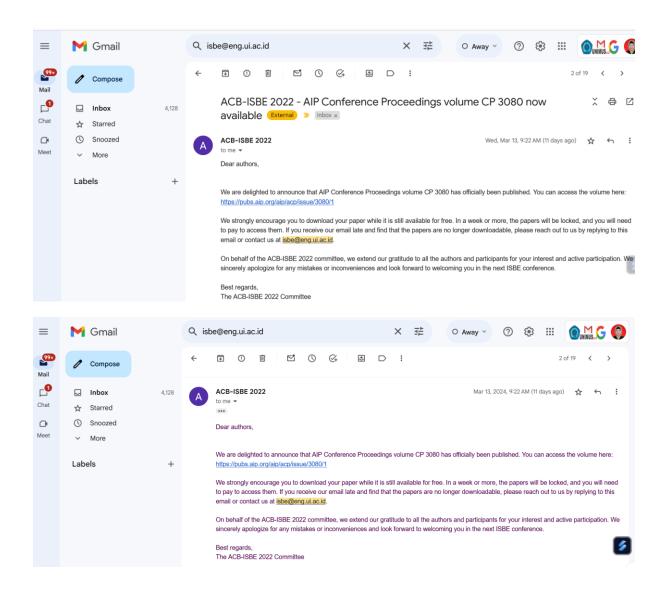
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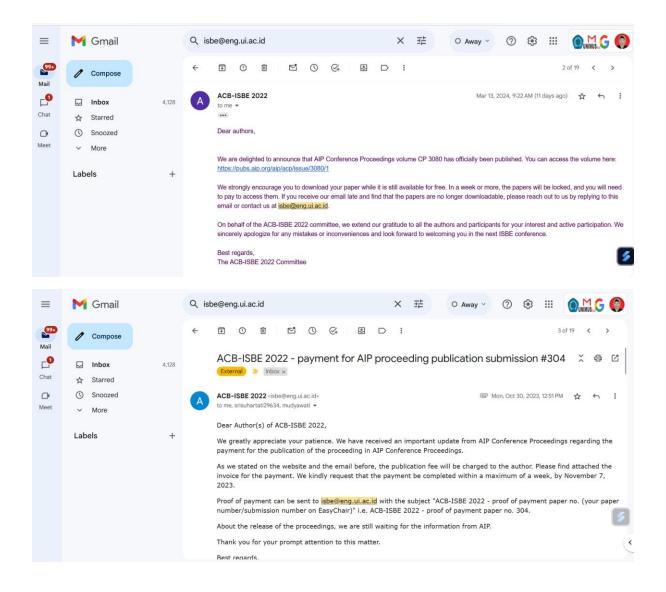
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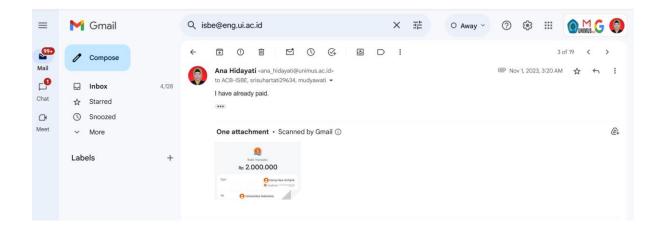
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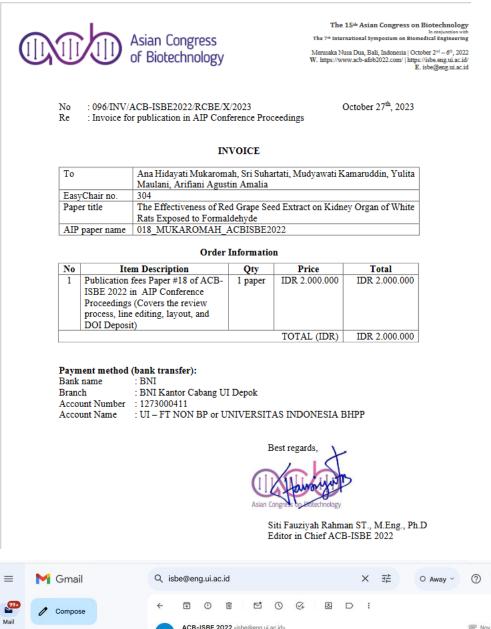
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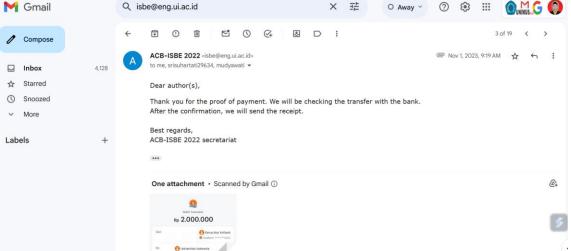


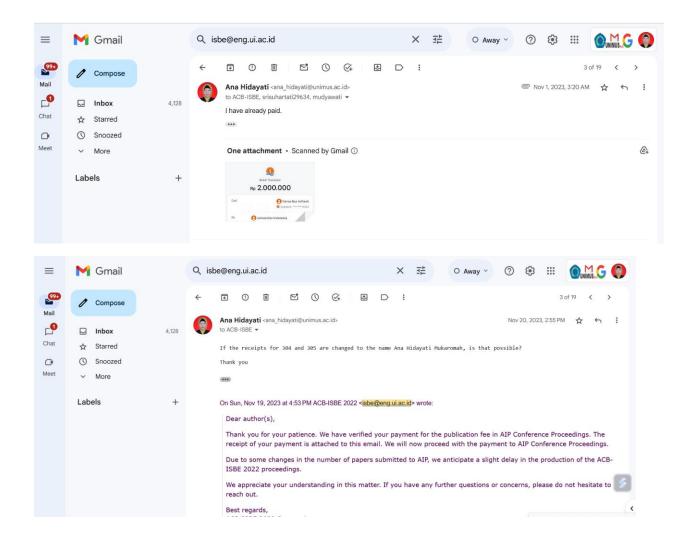


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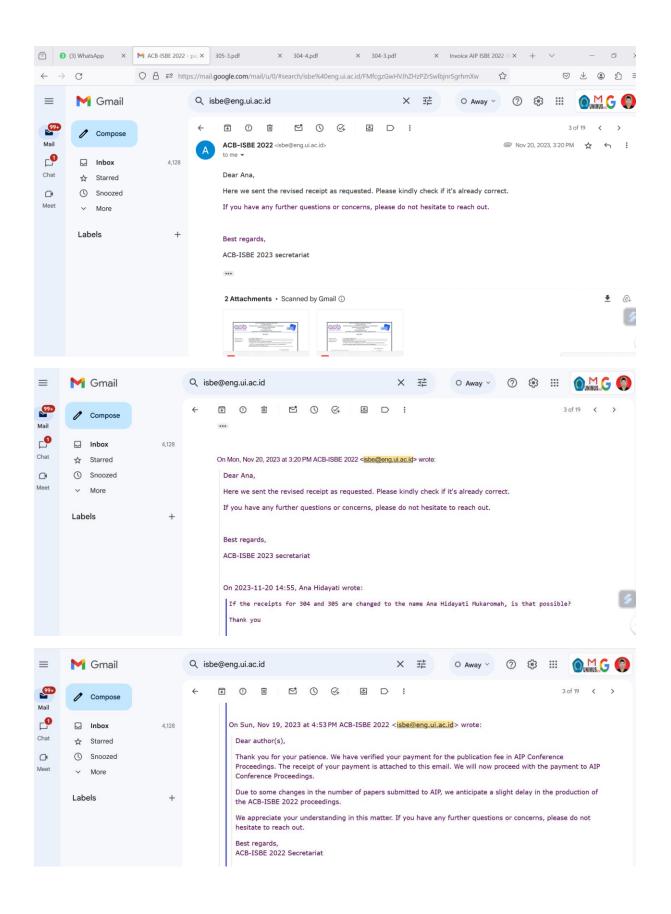
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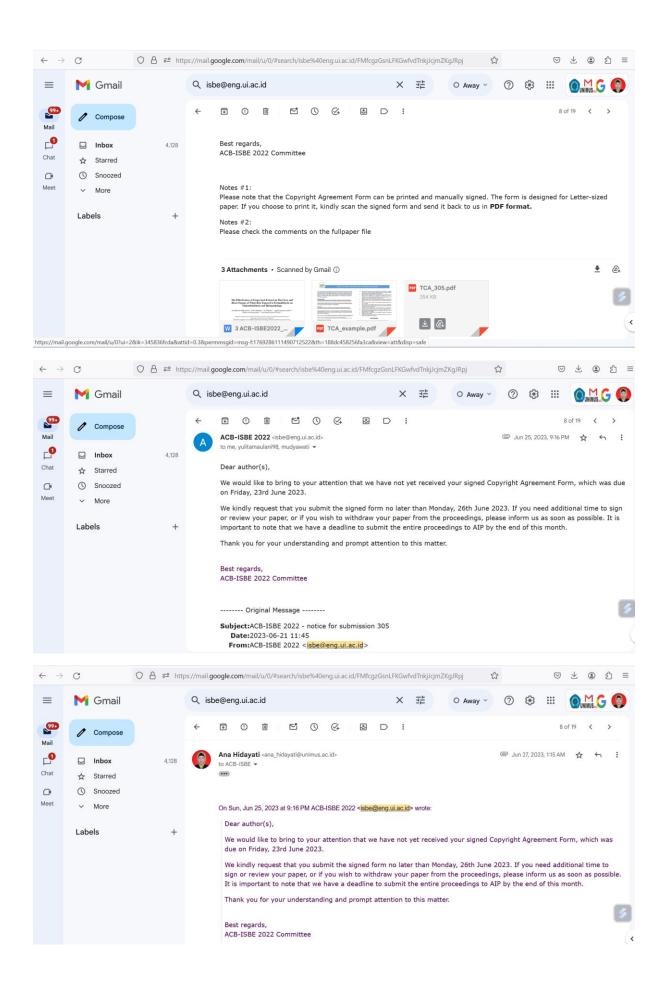


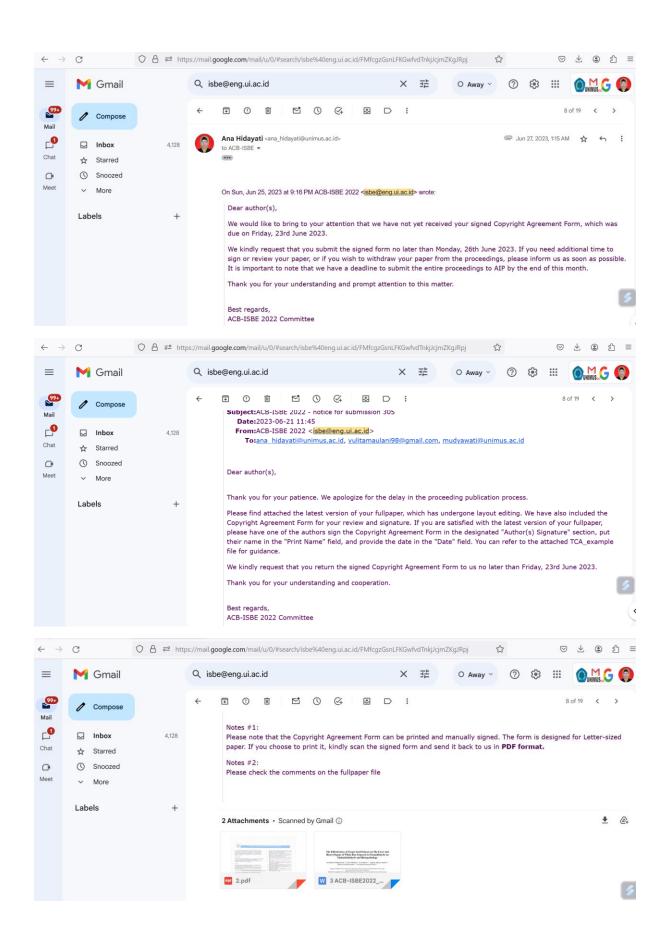
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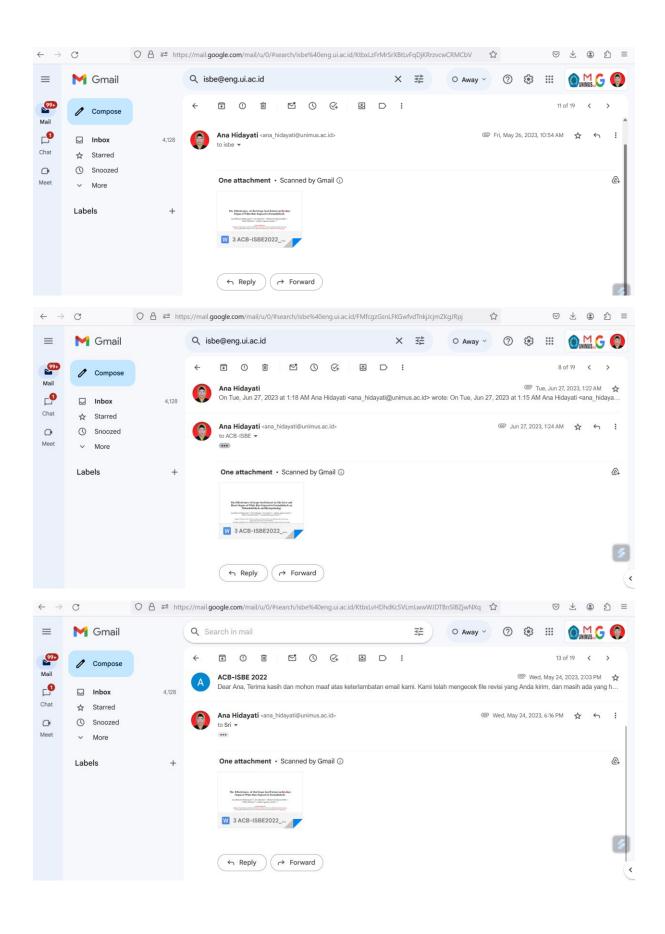


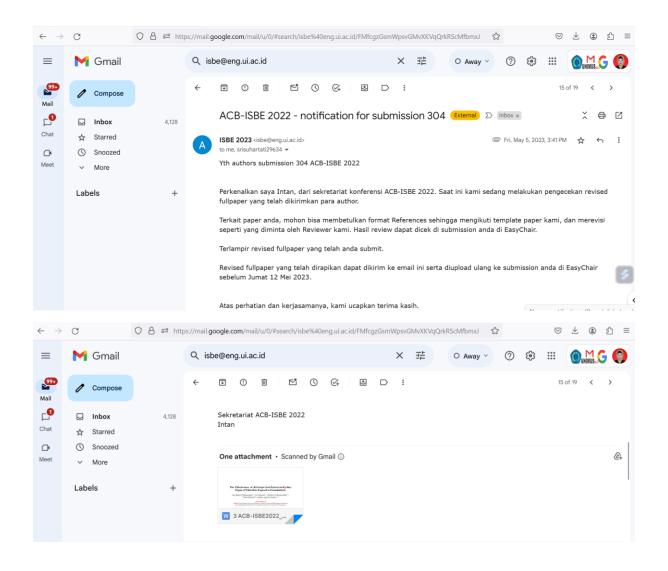


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			sign or review your paper, or if you wish to withdraw you	We kindly request that you submit the signed form no later than Monday, 26th June 2023. If you need additional time to sign or review your paper, or if you wish to withdraw your paper from the proceedings, please inform us as soon as possible. It is important to note that we have a deadline to submit the entire proceedings to AIP by the end of this month.											
			Thank you for your understanding and prompt attention	to this matter.											
			Best regards, ACB-ISBE 2022 Committee	(*											

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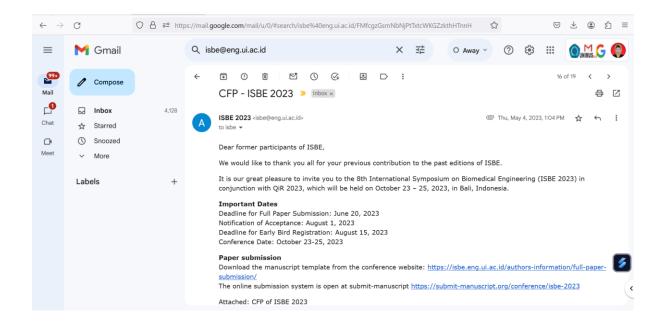




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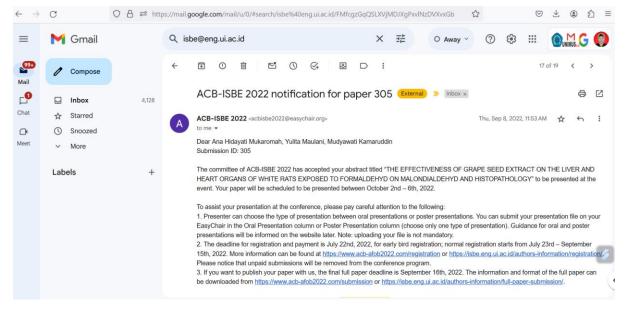
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			Terlampir revised fullpaper yang telah anda submit. Revised fullpaper yang telah dirapikan dapat dikirim ke email ini serta diupload ulang ke submission anda di EasyChair sebelum Jumat 12 Mei 2023.										
			Atas perhatian dan kerjasamanya, kami ucapkan terima kasih.										
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