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Research Article

THE EFFECT OF NANOEMULGEL RED ALGAE (*Eucheuma cottonii*) ON CYTOKINE IL-1 BETA EXPRESSION FOR TRAUMATIC ULCERS HEALING

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Abstract

Background: *Red algae (Eucheuma cottonii) is a type of seaweed (Rhodophyceae). Eucheuma cottonii contains flavonoids and florotanin as an anti-inflammatory agent. The extracted red algae were formulated into nanoemulgel. This study aimed to determine the effect of red algae nanoemulgel (Eucheuma cottonii) in the expression of IL-1β cytokines on the healing of traumatic ulcers.* ***Method:*** *Experimental research (post-test only control group design) was applied by the researcher. This research was conducted by giving Eucheuma cottonii nanoemulgel concentration of 20%, 35%, 50%, positive control and negative control at labial once a day, followed by evaluation using IHC method* ***Result:*** *The results revealed that Eucheuma cottonii nanoemulgel extract affected the expression of IL-1β cytokines in healing traumatic ulcers by decreasing the amount of IL-1β cytokine expression. In the one-way ANOVA test, the value of p = 0.00 (p 0.05) showed a significant difference for all groups. LSD (Least Significant Difference) post hoc test was conducted between 20% and 50% treatment groups, 20% treatment group and negative control, 35% treatment group and negative control, 50% treatment group and negative control, and positive control and negative control. The results obtained a p-value of 0.05, which indicates a significant difference in the expression of the number of IL-1β cytokines in traumatic ulcers between the two groups.* ***Conclusion:*** *The conclusion of this study was that the 20% Eucheuma cottonii extract nanoemulgel treatment group affected the amount of IL-1β by decreasing the expression of IL-1β cytokines. Nanoemulgel Eucheuma cottonii 20% is considered effective as an anti-inflammatory material.*

Keywords: Red algae (*Eucheuma cottonii);* nanoemulgels; cytokine; traumatic ulcer

INTRODUCTION

An ulcer is a pathological state characterized by a loss of epithelial tissue preceded by vesicles or bulae indicating the presence of an imbalance in the oral cavity[1]. Ulcers in the oral cavity often occur in women aged 16-25 years and rarely occur at the age of 55 years[2]. The prevalence of traumatic ulcers occur variably in several

countries, in Thailand 13.2% and Malaysia 12.4%[3].

The etiopathogenesis of the ulcer is still not clearly known, but these lesions can appear due to several factors such as genetic viral and bacterial infections, food allergies, vitamin deficiencies, stress and mechanical injuries. Ulcers that appear due to chemical, mechanical, physical and other pathological injuries are called traumatic ulcers. The initial stage of the appearance of lesions begins with the formation of ulcers and the release of pro-inflammatory cytokines, monocytes T and lymphocytes in mast cells as well as plasma cells accumulated in basal cells. In the next stage polynuclear leukocytes will dominate the central ulcer and on the boundary part of the lesion formed by the accumulation of mononuclear cells [4,5].

There are three stages of healing a traumatic ulcer: inflammation, proliferation and maturation. The initial stage of the inflammatory phase is characterized by the appearance of ulcers on the surface of the mucosa and an increase in pro-inflammatory cytokines and activating immune cells in the area of infection. The increasing number of pro-inflammatory cytokines can cause tissue damage, hence the body needs anti-inflammatory cytokines to compensate for the number of pro-inflammatory cytokines[6]. Pro inflammatory cytokines are produced by macrophages that have been activated and involved in the occurrence of inflammation. Proinflammatory cytokines include IL-1, β IL-6, and TNF-α which are secreted by neutrophils[7,8]. IL-1β is part of IL-1 which also consists of IL-1α. IL-1β is also a powerful proinflammatory cytokine and plays a role in the inflammatory process, which will destroy the rest of the extracellular matrix, release proteases and be stimulated by lymphocytes, macrophages and monocytes[8,9]. Anti-inflammatory cytokines are needed to balance the production of cytokines that cause inflammation so that inflammation can run well. Anti-inflammatory cytokines produced by the body are IL-10 and TGF-β which function to inhibit the production of pro-inflammatory cytokines (TNF, IL-1, chemokines, and IL-12) and inhibit macrophage function by suppressing the expression of MHC-II and dendritic cells for T-cell activation[6].

Indonesia is a maritime country that has many biological sources sourced from the sea such as seaweed. Seaweed is divided into four types, namely *Chlorophyceae* (green algae), *Rhodophyceae* (red algae), *Cynophyceae* (blue algae), and *Phaeophyceae* (brown algae)[10]. Seaweed has bioactive components such as sulfate polysaccharides including laminaran, carrageenan, fucoidan, and ulvan, as well as flavonoids, especially florotanins, carotenoids, especially fucoxanthin, galkaktan sulfta and ketin[11]. In addition, red algae (*Eucheuma cottonii*) can also produce carrageenan as a polysaccharide that can be used as an antibacterial, antiinflammatory, and antipyretic[12]. Extract of 20% *Eucheuma cottonii* is more effective in the wound healing process.

Most of these traumatic ulcers are often cured with therapeutic drugs for pain relief, therapeutic drugs for traumatic ulcers are usually available in the topical dosage form. Topical preparations have the disadvantage that particles are larger in size and have slower penetration. So it is necessary to develop other preparations such as nanoemulgel[14]. Nanoemulgel is an emulgel preparation made with a nanotechnology system and has small particles[15] . The smaller it is easier to dissolve in liquids to accommodate partitions in the oral mucosa. Therefore, it can be concluded that nanoemulgel preparations have a higher penetration rate into the oral mucosa compared to other preparations such as gels[16]. For the nanoemulgel formulation, *Eucheuma cottonii* will be washed and ground until smooth and then soaked in an alcohol solution. Then it was filtered to separate *Eucheuma cottonii* powder from *Eucheuma*

cottonii alcohol extract. Islam forbids its followers to consume alcohol, but there are studies which state that the use of alcohol is permissible. This is allowed if the alcohol is formed naturally through the fermentation process and the alcohol produced by anaerobic fermentation has a content of around 1%-15%. The alcohol is considered non-halal (haram) but is permissible for the industry and production of non-drinking drugs.[17].

MATERIAL AND METHODE

The type of research carried out is experimental analytical research using post-test only control group design. This study was conducted by giving *Eucheuma cottonii* nanoemulgel concentration of 20%, 35%, 50%, positive control and negative control in each group to determine the amount of IL-1β.

The ingredients used in this study include male Wistar rats, red algae (*Eucheuma cottonii),* ethanol, ketamine, aquadest, *palm oil*, tween 80, hematoxyline mayer, propyllenglikol, carbopol 940, methyl parapean, propyl parabean, *neutral* buffer formalin 10%, primary antibody IL-1β, secondary antibody IL-1β, HCl, xylol, nipasol, aquadest, glycerin, methanol, $FeCl_3$ and nipagin. Meanwhile the tools used in this research include: shakers, scales, stirrers, round burnishers, Bunsen spirtus burners, surgical scissors, microscopes, glass objects, and ultrasonic stirrers.

The first step taken in this study was to make nenoemulsion of red algae extract which had been extracted by the maceration method of 250 grams using methanol as much as 1000 ml[18]. The manufacture of nanoemulsions is divided into 3 phases, namely the oil phase, the water phase, and the surfactant phase. The water phase is formed by mixing red algae extract with palm oil and 10 grams of propylene glycol, 0.1 grams of methyl parabean and 0.02 propyl parabean and mixing using magnetic strirer at a speed of 1000 rpm for 2 hours. The next stage mixes 3.6 grams of tween 80 as surfactant and aquadest as solvent and ethanol using a homogenizer for 2 hours at a speed of 2000 rpm at a temperature of 30° to form a phase water. After the water phase temperature decreases, it is carried out by entering the oil phase using the titration method using a mechanical stirer for 6 minutes at 2000 rpm and continued by stirring for 25 min using an ultrasonicator until homogenous[16].

After making the nanoemulsion, it was continued with the making of nanoemulgel. Then, nanoemulgel was done by mixing the gel base and the red algae extract nanoemulsion. The gel base was prepared by mixing 0.1 gram of methyl parabean and 0.05 gram of propyl parabean into distilled water (aquadest). After that, mixing 2 grams of carbopol 940 into a measuring cup and continuing to insert TEA using a pipette until a gel base is formed. Insert the red algae extract nanoemulsion into the gel base and stirring using a *stirrer* at 500 rpm for 15 minutes[16].

The grouping of samples is carried out by dividing 5 groups as follows:

I. Red algae nanoemulgel treatment group 20%
II. Red algae nanoemulgel treatment group 35%
III. Red algae nanoemulgel treatment group 50%
IV. Positive control group with hyaluronic acid gel
V. Negative Control group

Making traumatic ulcers in experimental animals was carried out by anesthetizing the experimental animals using ketamine which was injected intramuscularly in experimental animals. Experimental animals that are already moving less actively, on the oral mucosa of the experimental animal have touched round burnisher that has been heated for 10 minutes on Bunsen spirtus. Observations were made at 24 hours and 48 hours post-ulcer making[19]. The procedure for applying red algae nanoemulgel was carried out as

much as 1x a day for 3 days after the formation of ulcer[20].

IHC staining is carried out by making tissue preparate which is deparaffinated and stained indirectly using *Bioss* brand IL-1 antibodies and βtissue reading and analysis are carried out using microscope[21]. This research has received approval from the Health and Medical Research Ethics Commission of the Faculty of Dentistry, Sultan Agung Islamic University, Semarang. Researchers conducted at the Bionanotechnology Laboratory of Diponegoro University (UNDIP), the Experimental Animal Laboratory of the Faculty of Medicine, Sultan Agung Islamic University (UNISSULA), the Anatomy Pathology Laboratory of the Hospital Islam Sultan Agung (RSISA), and the Laboratory of Anatomical Pathology of Sebelas Maret University (UNS).

RESULT

The results showed IL-1β expressions from labial preparate per group.

Traumatic ulcers are observed at 24 hours and 48 hours post-treatment until an ulcer with a yellowish base is formed. After the ulcer is formed, the smearing of nanoemulgel is carried out in the morning for 3 days. Tissue retrieval in experimental animals is carried out by dislocation of the neck in experimental animals, then cutting the oral mucosa of the experimental animal that has formed an ulcer. The ulcer sample that has been obtained is put in formalin for 3 days and then paraffin block is performed. After the formation of paraffin blocks, the manufacture of histological preparations and IHC staining is carried out. Figure 2 shows the expression of the IL-1β cytokine observed using a microscope with a magnification of 400x and 5 field of view. The average number of IL-1β cytokines obtained in the study is presented in figure 1 below:

Table 1. The average number of cytokines

	Group	Mean ± SD
IL-1β	I	4,87 ± 2,87
	II	11,01 ± 7,53
	III	17,09 ± 6,63
	IV	12,52 ± 5,09
	V	28,49 ± 7,20

Based on figure 1, it is known that the 20% *Eucheuma cottonii* extract nanoemulgel treatment group had the least amount of IL-1β cytokine expression. The negative control group got the highest number of IL-1β cytokine expressions.

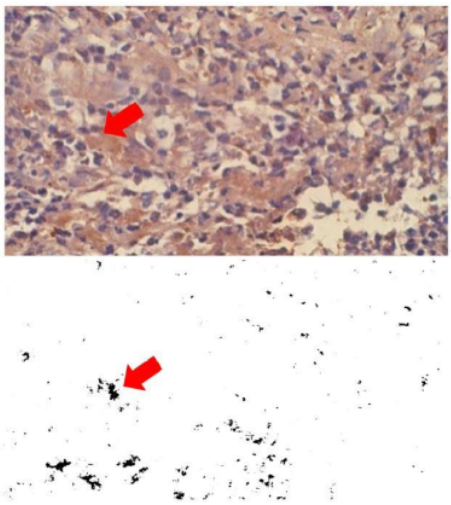

Figure 1. Histologic overview of the Nanoemulgel *Eucheuma cottonii* extract 20% treatment group using a microscope magnification 400x. Red arrow: expression of IL-1β cytokines (purple and coccus-shaped).

Meanwhile, figure 3 shows a comparison of the histological picture with a magnification of 40x, 100x, 400x and shows damaged tissue and healthy tissue.

Table 2. Normality Test Analysis Results (Shapiro-Wilk)

	Group	*Shapiro-Wilk*
IL-1β	I	0,192
	II	0,174
	III	0,932
	IV	0,148
	V	0,404

The normality test can be seen in table 1 which shows the results that the Nanoemulgel Eucheuma cottonii extract group 20%, Nanoemulgel *Eucheuma cottonii* extract 35%, Nanoemulgel *Eucheuma cottonii extract* 50%, the positive control group and the negative group have a p>0.005 value indicating normal distributed data.

Table 3. Homogeneity Test Analysis Results (Levene Test)

	Statistics	*Levene Test*
IL-1β	Based on average value	0,417

The results of the homogeneity test can be seen in table 2. The homogeneity test results showed p>0.005 (p = 0.417) so that the results showed that the results of the study carried out were homogeneous. Based on the normality and homogeneity test, homogeneous data were obtained and all groups were distributed normally, the hypothesis test was carried out using the *One-Way ANOVA* parametric test.

Table 4. Analysis Results of Different Tests in Groups (One Way Anova)

IL-1β	*I*	*II*	*III*	IV	V
I		0,128	**0,005**	0,062	0,000
II	0,128		0,132	0,701	0,000
III	0,005	0,132		0,252	0,008
IV	0,062	0,702	0,252		0,001
V	**0,000**	**0,000**	**0,008**	**0,001**	

The results of the *One-Way Anova* test can be seen in table 3 which shows the value of p<0.05 (p=0.000) that there is a significant difference in the expression of the IL-1β cytokine between the study groups. Furthermore, *a Post Hoc LSD (Least Significant Difference)* test was carried out to determine the differences between the 2 experimental groups.

Table 5. Results of Differential Test Analysis between 2 Groups (Post Hoc LSD)

	Group	*One Way Anova*
IL-1β	I	
	II	
	III	0,000
	IV	
	V	

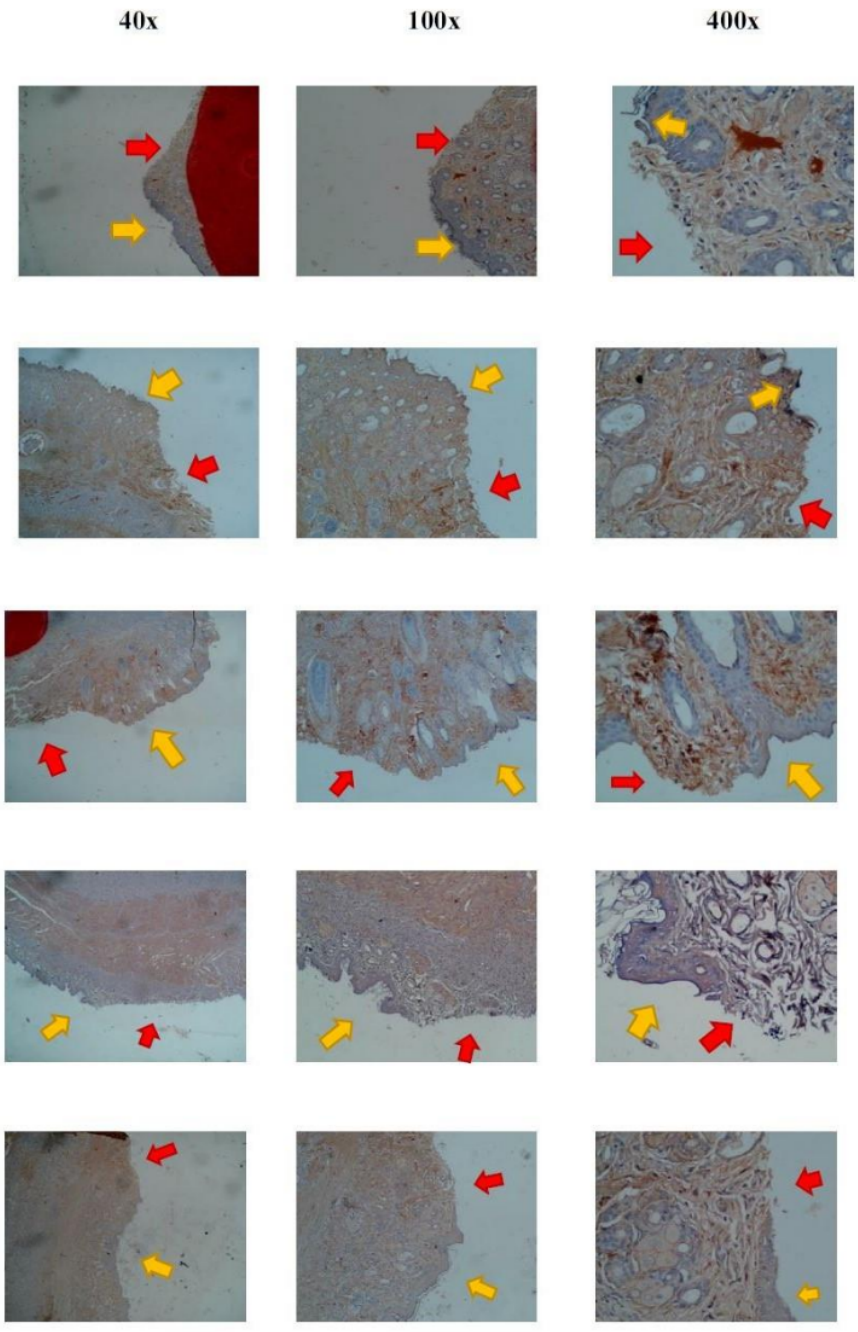

Figure 2. Histological overview of IHC magnification of 40x, 100x, and 400x. The figure shows the difference between damaged tissue which loses its epithelium shown in yellow arrows and healthy tissue which is shown by red arrows.

Post Hoc LSD test results can be seen in Table 4 The results of intergroup treatment tests on the expression value of the amount of cytokine IL-1β were obtained:

1. Between the treatment groups *Eucheuma cottonii* extract 20% and *Eucheuma cottonii extract 50%* obtained results p = 0.005 (p<0.05) which means that there was a significant difference in the expression value of cytokine IL-1β.
2. Between the *20% Eucheuma cottonii extract* treatment group and the negative control group, a result of p = 0.000 (p<0.05) was obtained, which meant that there was a significant difference in the expression value of the IL-1β cytokine.
3. Between the *35% Eucheuma cottonii extract* treatment group and the negative control group, a result of p=0.000 (p<0.05) was obtained, which meant that there was a significant difference in the expression value of the IL-1β cytokine.
4. Between the *50% Eucheuma cottonii* extract treatment group and the negative control group, a result of p=0.008 (p<0.05) was obtained, which meant that there was a significant difference in the expression value of the IL-1β cytokine.
5. Between the positive control group and the negative control group, a result of p=0.001 (p<0.05) was obtained, which means that there was a significant difference in the expression value of the cytokine IL-1β.

Table 6. Cumulative Results of Particle Size Analyzer (PSA) Test

PSA Test Cumulative Results	
Z-Avg	15,11 nm
PI	0,257 nm

Table 5 showed that the average size of nanoparticles in nanoemulsions is 15.11 nm with a PI value of 0.257.

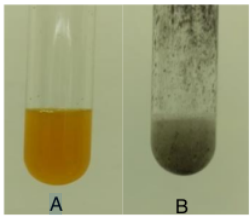

Figure 3. Test results of flavonoids (A) and tannins (B) assay.

The results of the assay of flavonoids and tannins (Figure 4) indicated that the preparation positively contained flavonoids (Figure 4.A) and tannins (Figure 4,B).

DISCUSSION

Based on the results of the study, the administration of nanoemulgel extract *Eucheuma cottonii* can affect the amount of cytokine IL-1β in traumatic ulcers. The results of data analysis in figure 4.1 showed that the average number of IL-1β cytokines in the Nanoemulgel Eucheuma cottonii extract 20% treatment group was 4.87, the Nanoemulgel Eucheuma cottonii extract 35% treatment group was 11.01, the Nanoemulgel *Eucheuma cottonii* extract 50% treatment group was 17.09, the positive control group was 12.52, and the negative control group was 28.49. Based on these results, the the highest number of IL-1β cytokines was obtained in the negative control group. Meanwhile, the control group of *Eucheuma cottonii* extract nanoemulgel 20% had the least amount of IL-1β cytokine expression.

Traumatic ulcers can be cured with topical medications such as hyaluronic acid and using herbal ingredients such as *Eucheuma cottonii* which contains flavonoids and florotanins as anti-inflammatory[22,23].

In this study, the use of nanoemulgel *Eucheuma cottonii 20%, nanoemulgel Eucheuma cottonii 35%* and positive control influenced the expression of

cytokine IL-1β as an anti-inflammatory by reducing the number of inflammatory cells in the extracellular matrix, allow cell migration and increase proliferation[23,24]. Nanoemulgel *Eucheuma cottonii* is more effective at reducing the amount of IL-1β cytokines compared to positive controls by giving hyaluronic acid gel because the use of nanoemulgel preparations in *Eucheuma cottonii* extract affects the wound healing process because it has nano-sized particles and good adhesive properties so that it can help drug penetration in the oral mucosa[23]. In addition, nanoemulgel extract with a concentration of 20% is more effective in the wound healing process compared to nanoemulgel with a higher concentration. According to previous research, the concentration levels of concentration levels of ethanol extract cannot be used as an appropriate reference in the process of wound healing. This is related to the nature of the preparation that affects penetration into the wound in the oral mucosa[24].

The average size of nanoparticles in nanoemulsions can be seen in table 4.5. It showed that the distribution mean of nanoparticles size is 15.11 nm with a PI value of 0.257. Based on research which stated that the poly states that the polydispersity index (PI) value that is close to zero indicates the uniformity of globule size in the preparation is getting higher[25]. The PSA test obtained a size distribution value based on intensity in nanoemulsions ranging from 5.615 nm to 43.82 nm. This is in line with previous research which stated that dynamically nenoemulsion as a stable and transparent emulsion has a particle size range of 5-200 nm[26].

The *one-way ANOVA* test showed a value of P=0.000 (P<0.05), which means that there were differences between the treatment groups of *Eucheuma cottonii* extract nanoemulgel 20%, 35%, 50%, the positive control group (*hyaluronic acid),* and the negative control group. LSD test results showed that there was a significant difference between the negative control group to the 20% treatment group and the 20% to 50% treatment group. This is due to the 50% preparation sample has a more stable viscosity which affects the penetration of the nanoemulgel into the oral mucosa. The 20% and 35% treatment groups did not have a significant difference because the viscosity of the preparation which was almost resemblant. Hence, it could affect the penetration properties of the oral mucosa. In addition, the higher viscosity value has better stability[26].

This study showed that there was an influence of *Eucheuma cottonii* nenoemulgel on the expression of IL-1β cytokines on the healing of traumatic ulcers.

CONCLUSION

Based on the research that has been carried out, it can be concluded as follow:

1. The administration of *Eucheuma cottonii* nanoemulgels that affect the number of cytokines IL-1β by lowering IL-1β shows that *Eucheuma cottonii* nanoemulgels act as anti-inflammatory.
2. The administration of *Eucheuma cottonii* nanoemulgels on day 4 showed that *Eucheuma cottonii* nanoemulgels were 20% more effective at reducing the expression of cytokines IL-1β compared to concentrations of 35% and 50%.
3. The administration of nanoemulgels of 20% and 35% is more effective at reducing the expression of cytokine IL-1β compared to the administration of hyaluronic acid *gel*. Meanwhile, the administration of hyaluronic acid gel is more effective at reducing IL-1β compared to *Eucheuma cottonii* nanoemulgels *by 50%*.
4. Negative control with no treatment in experimental animals showed the highest expression value of cytokine IL-1β.

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THE EFFECT OF NANOEMULGEL RED ALGAE (Eucheuma cottonii) ON CYTOKINE IL-1 BETA EXPRESSION FOR TRAUMATIC ULCERS HEALING

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GRADEMARK REPORT

FINAL GRADE

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GENERAL COMMENTS

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RUBRIC: 6TH-8TH SCIENCE ARGUMENT (CER)

CLAIM

Take an arguable position on the scientific topic and develop the essay around that stance.

ADVANCED	The essay introduces a precise, qualitative and/or quantitative claim based on the scientific topic or text(s), regarding the relationship between dependent and independent variables. The essay develops the claim and counterclaim fairly, distinguishing the claim from alternate or opposing claims.
PROFICIENT	The essay introduces a clear, qualitative and/or quantitative claim based on the scientific topic or text(s), regarding the relationship between dependent and independent variables. The essay effectively acknowledges and distinguishes the claim from alternate or opposing claims.
DEVELOPING	The essay attempts to introduce a qualitative and/or quantitative claim, based on the scientific topic or text(s), but it may be somewhat unclear or not maintained throughout the essay. The essay may not clearly acknowledge or distinguish the claim from alternate or opposing claims.
EMERGING	The essay does not clearly make a claim based on the scientific topic or text(s), or the claim is overly simplistic or vague. The essay does not acknowledge or distinguish counterclaims.

EVIDENCE

Include relevant facts, definitions, and examples to back up the claim.

ADVANCED	The essay supplies sufficient relevant, accurate qualitative and/or quantitative data and evidence related to the scientific topic or text(s) to support its claim and counterclaim.
PROFICIENT	The essay supplies relevant, accurate qualitative and/or quantitative data and evidence related to the scientific topic or text(s) to support its claim and counterclaim.
DEVELOPING	The essay supplies some qualitative and/or quantitative data and evidence, but it may not be closely related to the scientific topic or text(s), or the support that is offered relies mostly on summary of the source(s), thereby not effectively supporting the essay's claim and counterclaim.
EMERGING	The essay supplies very little or no data and evidence to support its claim and counterclaim, or the evidence that is provided is not clear or relevant.

REASONING

Explain how or why each piece of evidence supports the claim.

ADVANCED	The essay effectively applies scientific ideas and principles in order to explain how or why the cited evidence supports the claim. The essay demonstrates consistently logical reasoning and understanding of the scientific topic and/or text(s). The essay's explanations anticipate the audience's knowledge level and concerns about this scientific topic.

PROFICIENT	The essay applies scientific reasoning in order to explain how or why the cited evidence supports the claim. The essay demonstrates logical reasoning and understanding of the scientific topic and/or text(s). The essay's explanations attempt to anticipate the audience's knowledge level and concerns about this scientific topic.
DEVELOPING	The essay includes some reasoning and understanding of the scientific topic and/or text(s), but it does not effectively apply scientific ideas or principles to explain how or why the evidence supports the claim.
EMERGING	The essay does not demonstrate clear or relevant reasoning to support the claim or to demonstrate an understanding of the scientific topic and/or text(s).

FOCUS

Focus your writing on the prompt and task.

ADVANCED	The essay maintains strong focus on the purpose and task, using the whole essay to support and develop the claim and counterclaims evenly while thoroughly addressing the demands of the prompt.
PROFICIENT	The essay addresses the demands of the prompt and is mostly focused on the purpose and task. The essay may not acknowledge the claim and counterclaims evenly throughout.
DEVELOPING	The essay may not fully address the demands of the prompt or stay focused on the purpose and task. The writing may stray significantly off topic at times, and introduce the writer's bias occasionally, making it difficult to follow the central claim at times.
EMERGING	The essay does not maintain focus on purpose or task.

ORGANIZATION

Organize your writing in a logical sequence.

ADVANCED	The essay incorporates an organizational structure throughout that establishes clear relationships among the claim(s), counterclaims, reasons, and evidence. Effective transitional words and phrases are included to clarify the relationships between and among ideas (i.e. claim and reasons, reasons and evidence, claim and counterclaim) in a way that strengthens the argument. The essay includes an introduction and conclusion that effectively follows from and supports the argument presented.
PROFICIENT	The essay incorporates an organizational structure with clear transitional words and phrases that show the relationship between and among ideas. The essay includes a progression of ideas from beginning to end, including an introduction and concluding statement or section that follows from and supports the argument presented.
DEVELOPING	The essay uses a basic organizational structure and minimal transitional words and phrases, though relationships between and among ideas are not consistently

	clear. The essay moves from beginning to end; however, an introduction and/or conclusion may not be clearly evident.
EMERGING	The essay does not have an organizational structure and may simply offer a series of ideas without any clear transitions or connections. An introduction and conclusion are not evident.

LANGUAGE

Pay close attention to your tone, style, word choice, and sentence structure when writing.

ADVANCED	The essay effectively establishes and maintains a formal style and objective tone and incorporates language that anticipates the reader's knowledge level and concerns. The essay consistently demonstrates a clear command of conventions, while also employing discipline-specific word choices and varied sentence structure.
PROFICIENT	The essay generally establishes and maintains a formal style with few possible exceptions and incorporates language that anticipates the reader's knowledge level and concerns. The essay demonstrates a general command of conventions, while also employing discipline-specific word choices and some variety in sentence structure.
DEVELOPING	The essay does not maintain a formal style consistently and incorporates language that may not show an awareness of the reader's knowledge or concerns. The essay may contain errors in conventions that interfere with meaning. Some attempts at discipline-specific word choices are made, and sentence structure may not vary often.
EMERGING	The essay employs language that is inappropriate for the audience and is not formal in style. The essay may contain pervasive errors in conventions that interfere with meaning, word choice is not discipline-specific, and sentence structures are simplistic and unvaried.