The Effect Of Giving Clove (*Syzygium Aromaticum*) On Pancreatic Function And Pancreatic Histopathology Of Male Wistar White Rats Infected By *Staphylococcus Aureus* Bacteria

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ABSTRACT

Infection is still a health problem for developed and developing countries. The pancreas is one of the organs that often experiences infection. This study aims to analyze the effectiveness of giving clove extract (Syzygium aromaticum) on the pancreas function of male white rats (*Rattus norvegicus*) of the wistar strain infected with *Staphylococcus aureus* and how the histopathology is. The research sample was 24 male Wistar rats.

This study uses a quantitative experimental research type, namely by using a true experiment or laboratory experimental design. This study uses a post-test only control group design to determine and analyze the effects before and after administration of clove extract in improving pancreatic function in white rats (*Rattus norvegicus*) Wistar strain infected with *Staphylococcus aureus* bacteria. The results of the One-way Anova test on the results of observations of serum lipase and amylase levels showed a significance value of 0.000 or greater than 0.05. It was concluded that there was a significant difference between the control group, treatment group 1, treatment group 2, and treatment group 3. The Post Hoc LSD test showed that there was a significant difference between the control group and treatment group 1 ($p = 0.000$) and treatment group 2 ($p = 0.000$). There was no significant difference between the control group and treatment group 3 ($p = 0.475$). Clove extract contains secondary metabolites in the form of saponins, tannins, flavonoids, and triterpenoids that help repair damaged pancreatic cells due to Staphylococcus aureus infection. Administration of clove extract at a dose of 600 mg/kgBW is effective in improving pancreatic function in white rats (Rattus norvegicus) Wistar strain that experience Staphylococcus aureus infection. The results of histopathological observations of pancreatic tissue in treatment group 3 (600 mg/kgBW) experienced the most significant improvement and approached the control group (reference group) compared to other groups

Keywords: *Pancreas, Clove Extract, Staphylococcus aureus.*

INTRODUCTION

Staphylococcus aureus one of the types of pathogenic bacteria that often cause infections. The presence of Staphylococcus aureus in the bloodstream (bacteremia) can lead to the development of sepsis - a systemic inflammatory response to infection. A characteristic feature of sepsis is a paradoxical immunosuppressive response that sometimes occurs simultaneously with inflammation. This combination of inflammation and immunosuppression causes additional damage to local tissues and renders the body defenseless against the causative pathogen and secondary infections. The inflammatory response shifts the balance between pro- and anti-coagulation mechanisms, potentially leading to disseminated intravascular coagulation (DIC). DIC microthrombi develop in blood vessels, damaging the endothelium and obstructing blood flow, resulting in organ oxygen deprivation. Because this systemic coagulation depletes existing clotting factors, it is often followed by bleeding that further worsens organ injury (Gnanamani, 2017). Staphylococcus can cause disease due to its ability to divide and spread widely into tissues through the production of several extracellular materials, one of which is the pancreas organ. The pancreas is an additional digestive gland found retroperitoneally, across the vertebral bodies in the posterior abdominal wall. The pancreas is located transversely in the upper abdomen between the duodenum on the right and the spleen on the left. It is divided into head, neck, body, and tail. The head is located on the inferior vena cava and renal vein and is surrounded by the duodenal C-curvature. The tail of the pancreas extends to the hilum of the spleen. The pancreas produces exocrine secretions (pancreatic fluid from acinar cells) which then enter the duodenum through the main and accessory pancreatic ducts and endocrine secretions (glucagon and insulin from the pancreatic islets of Langerhans) which enter the blood (Talathi SS, 2023). Infection is still a health problem for both developed and developing countries. However, bacterial infections are more common in developing countries, with increasing infection and death rates. Antibiotics are used to destroy pathogenic bacteria without harming their hosts. Some bacteria are resistant to certain classes of antibiotics, either because they do not have a target or because they are immune to the drug (Fonggang, 2023). Staphylococcus can cause disease due to its ability to divide and spread widely into tissues through the production of several extracellular materials, one of which is the pancreas organ. The primary role of amylase is to break down glycosidic bonds in starch molecules, converting complex carbohydrates into simpler sugars. Amylase enzymes are categorized into 3 main classes – alpha, beta, and gamma amylases – each targeting a different segment of the carbohydrate molecule. Alpha amylase is found in humans, animals, plants, and microbes, while beta amylase is found primarily in microbes and plants. In contrast, gamma amylase can be found in both animals and plants (Akinfemiwa O, 2023). Lipases are a family of enzymes that break

down triglycerides into free fatty acids and glycerol. Some are expressed and active in many tissues; for example, hepatic lipase is found in the liver, hormone-sensitive lipase is found in adipocytes, lipoprotein lipase is found on the endothelial surface of blood vessels, and pancreatic lipase is found in the small intestine. Lipases in pancreatic secretions are responsible for the digestion and hydrolysis of fats and the absorption of fat-soluble vitamins. Understanding the function of lipases is essential for the pathophysiology of fat necrosis and acute and chronic pancreatitis. In addition, lipases also play an important role in the mechanism of action of several cholesterol-lowering drugs. Damage to the pancreas will disrupt the human digestive system, therefore treatment for bacterial infections is needed in the form of plants that are rich in antioxidants and can be antibacterial agents. One of them is the clove plant. Syzygium aromaticum commonly known as cloves, is a medium-sized tree (8 – 12 m) from the Myrtaceae family originating from the Maluku Islands in Eastern Indonesia. This oil has been known as a valuable trade spice for centuries and helps the economic development of the Asian region. Cloves are the dried flower buds of Syzygium aromaticum. Many bioactive compounds with antioxidant potential have been identified in cloves. The main components of essential oils are phenylpropanoids such as eugenol, eugenol acetate, carvacrol, thymol and cinnamaldehye. Cloves also contain non-volatile bioactive substances such as sterols, flavonoids, galloyl tannins, phenolic acids and triterpenes (Nikousaleh A, 2016). Previous research has shown that eugenol is the main component of clove extract which has antibacterial activity.

LITERATURE REVIEW

The pancreas is part of the digestive system that makes and secretes digestive enzymes into the intestines, and is also an endocrine organ that makes and secretes hormones into the blood to control metabolism and energy storage throughout the body (Longnecker, 2021). The pancreas produces many digestive enzymes, including pancreatic amylase, pancreatic lipase, trypsinogen, chymotrypsinogen, procarboxypeptidase, and proelastase. These enzymes are isolated from the acidic environment of the stomach and function optimally in the more alkaline environment of the small intestine, which has a pH of 6 to 7 due to bicarbonate secreted by the pancreas. Pancreatic amylase, like salivary amylase, digests starch into maltose and maltotriose. Pancreatic lipase, secreted by the pancreas with an important coenzyme called colipase, hydrolyzes the ester bonds in triglycerides to form diacylglycerols and monoacylglycerols (Patricia JJ, 2024). *Staphylococcus aureus*is a gram-positive bacterium and the causative agent of a variety of infectious diseases such as skin infections, bacteremia, endocarditis, pneumonia and food poisoning. This organism was initially a major nosocomial

pathogen and later epidemiologically distinct clones emerged in the community environment. *S. aureus* exhibits a number of virulence factors that aid in the establishment of infection by facilitating tissue attachment, tissue invasion and evasion of the host immune response. The ability to acquire resistance to multiple classes of antibiotics makes *S. aureus* a challenging pathogen to treat. The emergence and spread of methicillin-resistant strains of *S. aureus*, termed methicillin-resistant *S. aureus* (MRSA), has resulted in high morbidity, mortality and increased medical costs (Gnanamani, 2017). *Syzygium aromaticum*belongs to the Myrtaceae family which has more than 3000 species and 130–150 genera, such as the myrtle, eucalyptus, clove, and guava families. Clove is an aromatic flower cultivated in Madagascar, Sri Lanka, Indonesia, and China (Golmakani et al., 2017; Tunc & Koca, 2019) Several reports indicate that S.aromaticum L. contains about 15–20% by weight. Clove extract contains high amounts of phenolic compounds with several biological activities, including antibacterial, antifungal, insecticidal, and antioxidant properties(Haro, 2021)

The conceptual framework used in this study can be seen in Figure 1.

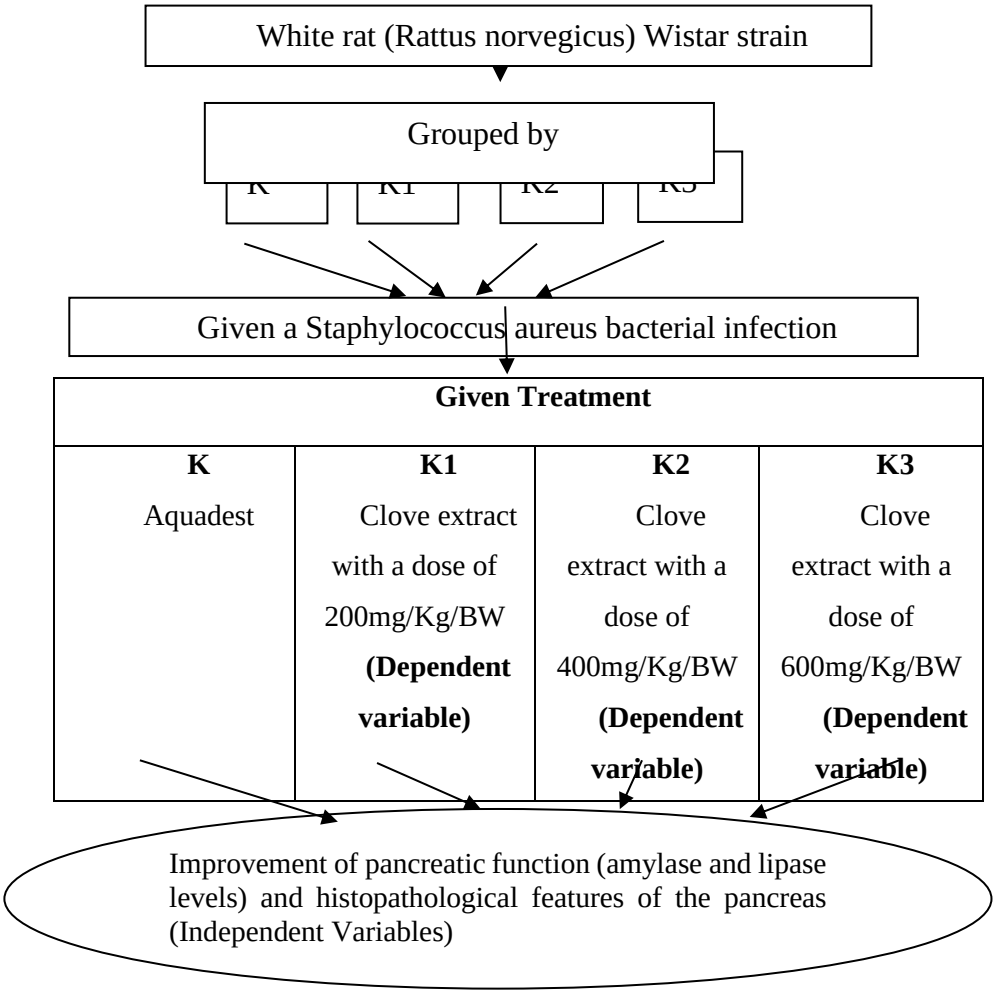


Figure 1 Conceptual Framework

METHODS

This study uses a type of experimental quantitative research, namely by using a true experiment or laboratory experimental design. True experiment is an experimental study that is carried out seriously by controlling all external variables that can affect experimental activities. This study uses a post-test only control group design to determine and analyze the effects before and after administration of clove extract in improving pancreatic function in white rats (*Rattus norvegicus*) Wistar strain infected with *Staphylococcus aureus* bacteria. This research was conducted at the Laboratory of the Department of Pharmacology and Therapeutics, Faculty of Medicine, University of North Sumatra and the Laboratory of Pathology Anatomy, University of North Sumatra. This research was conducted in June-August 2024. Ethical Clearance will be submitted to the Health Research Ethics Commission (KPEK) of Prima Indonesia University and is still in process. The sample of this study was male wistar rats (*Rattus norvegicus*) weighing 160 – 200 grams and aged 2 – 3 months. In this study, researchers used 24 wistar rats for each experimental group. The grouping of test animals was carried out randomly into 4 test groups.

Examination of Pancreatic Organ Function and Histopathology Observation Process of the Organ

Parameters for pancreatic function examination are amylase and lipase enzymes. Amylase works by hydrolyzing carbohydrates and forming simple sugars, while lipase works by hydrolyzing fats to form fatty acids. Amylase and lipase are enzymes secreted by the exocrine portion of the pancreas. Amylase and lipase levels are used as biochemical markers of pancreatic dysfunction. On the 15th day, the mice were anesthetized for further blood sampling through the orbital vein with a capillary pipette of 3 cc collected into an EDTA (EthylenediamineTetraacetic Acid) tube and placed in a cool box. The blood samples were then examined at the University of North Sumatra Laboratory to determine amylase and lipase levels. The pancreas was taken on the 14th day after the test animals went through the treatment process. The pancreas obtained was then cleaned and fixed with a solution (Bio Analitika Pro Analysis Formaline Buffer) 10% for at least 24 hours, then the pancreas sample was dehydrated with graded alcohol concentrations, followed by a clearing process using xylol, impregnation and block making (embedding) using paraffin. The block was cut 5µm thick with a microtome, then general Hematoxylin-Eosin (HE) staining was carried out (Nadya and Nurlita, 2013). Data from histopathological observations through microscopic examination were collected and then scored. The research data were tabulated, then the changes found were analyzed and presented descriptively. Data from observations of pancreatic function based on amylase and lipase levels were then analyzed using SPSS (Statistic of Package for Social

Science) 25.0 for windows. The data normality test was analyzed using the Kolmogorov-Smirnov test approach (p> 0.05). To test the significance between the trial groups, one-way analysis of variance or One Way ANOVA was used at a 95% confidence level (p <0.05). Further analysis or testing was carried out using the Post Hoc Test with the LSD technique.

RESULTS

This study used test animals in the form of male white rats (*Rattus norvegicus*) Wistar strain weighing 160 – 200 g aged 2 – 3 months. The test animals were divided into 4 groups, the control group was only given regular feed and distilled water, the treatment group was given an infection with a suspension of *Staphylococcus aureus* bacteria. and clove extract with different doses, namely 200 mg/KgBB, 400 mg/KgBB, and 600 mg/KgBB. The characteristics of the test animals can be seen in the table 1.

Table 1 Characteristics of test animals

Component	Group			
	Control	**P1**	**P2**	**P3**
Types of Rats	Wistar strain white rats			
Gender	Male			
General Condition	White fur color, healthy and active			
Average Initial Body Weight	192gr	189gr	190gr	178gr
Average Final Weight	190gr	188gr	189gr	177gr

Based on the characteristics of the test animals, in general the mice were in healthy condition during this study, namely before and after treatment. A total of 24 test animals were able to follow this study until the end without any drop outs. Weighing was carried out on the 24 test animals. The average body weight of each group before and after treatment for 14 days can be seen in the Table.

Results Description Specific Objectives

Based on the results of the phytochemical tests conducted, it can be concluded that clove extract (*Syzygium aromaticum*) contains secondary metabolites in the form of flavonoids, saponins, tannins, alkaloids, and steroids. The following are the screening results obtained can be seen table 2.

Table 2 Phytochemical Tests

Secondary Metabolites	Color	Results
Flavonoid	Yellow	+
Saponins	Yellow and foamy	+
Tannin	Blackish blue	+
Alkaloid	Yellow	+
Steroid	Green	+

Description: (+) = Contains the tested compound group

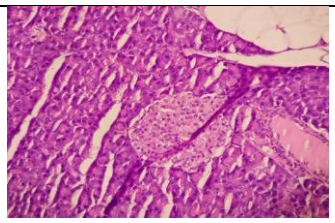
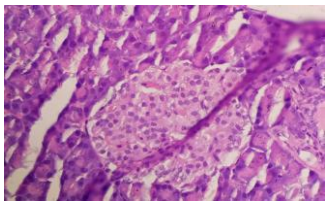
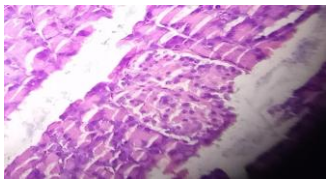
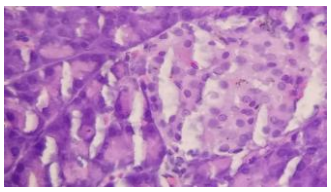
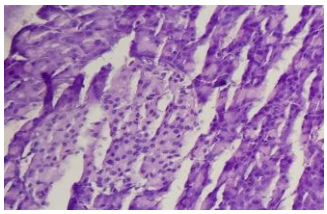
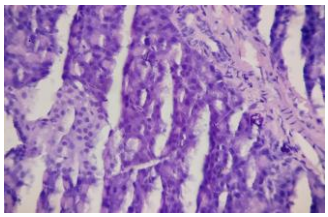
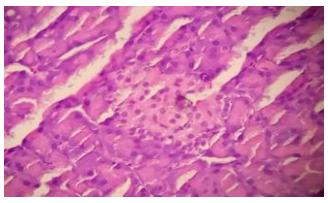
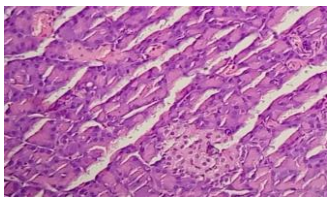
(-) = Does not contain the tested compound

Results of Observation of Serum Lipase and Amylase Levels

The results of observations made on all groups showed that there was a change in lipase levels in the treatment group. Based on the average lipase levels, it can be seen that the control group had an average value of 22.26 U/L before treatment and 14 days to 23.03 U/L. The lipase levels of mice in the control group are a reference for the high and low lipase levels in the treatment group. Treatment group 1 after being given a bacterial infection had a lipase level of 42.5 U/L and after being given clove extract at a dose of 200mg/KgBB it became 32.43 U/L. Treatment group 2 after bacterial infection 41.76 U/L and after being given clove extract at a dose of 400mg/KgBB it became 27.08 U/L. Finally, treatment group 3 after bacterial infection 42.3 U/L and after being given clove extract at a dose of 600mg/KgBB it became 23.55 U/L. Based on the difference in the average value of lipase levels, the researchers concluded that treatment group 3, namely mice infected with *Staphylococcus aureus* bacteria and given clove extract at a dose of 600 mg/kgBW had the greatest decrease in lipase levels and was close to the control group. While treatment group 1, which was given clove extract at a dose of 200 mg/kgBW experienced the lowest decrease or improvement in lipase levels compared to treatment groups 2 and 3. The results of observations made on all groups showed that there was a change in amylase levels in the treatment group. Based on the average amylase levels, it can be seen that the control group had an average value of 59.75 U/L before treatment and 60.85 U/L after being given distilled water for 14 days. The amylase levels of mice in the control group are used as a reference for the high and low levels in the treatment group. Treatment group 1 after being given a bacterial infection had an amylase level of 68.6 U/L and after being given clove extract at a dose of 200mg/KgBB it became 67.41U/L. Treatment group 2 after being infected with *Staphylococcus aureus* bacteria 67.9 U/L and after being given clove extract at a dose of 400 mg/KgBB it became 63.01U/L. Finally, treatment group 3 after bacterial infection was 68.53 U/L and after being given clove extract at a dose of 600mg/KgBW it became 60.61 U/L. Normality test data were obtained with the help of

SPSS using the Kolmogorov-Smirnov test. The results showed that the data for each group were normally distributed with a significance value of 0.200 in all test groups for testing serum lipase and amylase levels. So it can be concluded that the data is normally distributed, or can represent the population. The serum lipase and amylase levels were then tested for homogeneity using the Levene test to determine whether the data came from a population with the same variance. The results obtained showed a significance value of 0.694 for lipase levels and 0.526 for amylase levels. The probability value of significance obtained was greater than 0.05, so it can be concluded that the results of observations of serum lipase and amylase levels in the control group, treatment group 1, treatment group 2, and treatment group 3 were homogeneous or came from the same population. The normally distributed and homogeneous data were then tested for effectiveness and significance with the One-Way Anova test. The results of the One-way Anova test on the results of observations of serum lipase and amylase levels showed a significance value of 0.000 or greater than 0.05. Based on these data, it can be concluded that there is a significant difference between the control group, treatment group 1, treatment group 2, and treatment group 3 so that a further post-hoc LSD test is needed. The Post-hoc LSD test was conducted to analyze the differences in the average lipase and amylase between groups. The results of the analysis of serum lipase levels using the Post Hoc LSD Test were used to determine whether the group had a significant difference from the other groups. The results of the analysis showed that there was a significant difference between the control group and treatment group 1 ($p = 0.000$) and treatment group 2 ($p = 0.000$). There was no significant difference between the control group and treatment group 3 ($p = 0.475$). The results of the analysis of serum amylase levels using the Post Hoc LSD Test were used to determine whether the group had a significant difference in amylase from the other groups. The results of the analysis showed that there was a significant difference between the control group and treatment group 1 ($p = 0.000$). The control group and treatment group 2 obtained a significance value of 0.045. While the control group and treatment group 3 did not have a significant difference with a significance value of 0.821. Based on the difference in the average serum amylase levels, the researchers concluded that treatment group 3, namely mice infected with *Staphylococcus aureus* bacteria and given clove extract at a dose of 600 mg/kgBW, had the greatest decrease in serum amylase levels and was close to the control group. While treatment group 1, namely mice given clove extract at a dose of 200 mg/kgBW, experienced the least decrease or improvement in lipase levels. The following is a histological image of the pancreatic tissue of each treatment group can be seen at table 3.

Table 3 Histopathological Description of Pancreatic Tissue

No	Group	Histopathological Image of Pancreatic Tissue	
1	Control (Aquades)		
2	Treatment 1 (200mg/KgBW)		
3	Treatment 2 (400mg/KgBW)		
4	Treatment 3 (600mg/KgBW)		

The results of histopathological observations showed different cell appearances. The control group that did not experience infection had a normal pancreatic histology and was included in the score category 0. The histopathology of the pancreas in the control group was in normal form because it was not given a bacterial infection so it was used as a reference to describe other groups and as a comparison with the treatment group given a bacterial infection and clove extract. In treatment group 1 which was given a bacterial infection and clove extract at a dose of 200mg/KgBW, there was a difference in shape because the pancreas organ had been exposed to the consumption of bacterial infection which changed the histological structure of the mouse pancreas. All research subjects got a score of 4, namely necrosis of all pancreatic cells. Treatment group 2 which was given clove extract at a dose of 400 mg/kgBW showed improvements in the histological structure of the pancreas, namely 1 subject got a score of 0, 4 subjects got a score of 4, and 1 subject got a score of 2. Treatment group 3 which was given bacterial infection and clove extract at a dose of 600 mg/kgBW showed an improvement in

the histological structure of the pancreas that was close to the control group, namely 4 subjects got a score of 0 and 2 others got a score of 1.

DISCUSSION

This study was conducted to test and analyze the effectiveness of clove extract administration on the pancreas function of white rats (*Rattus norvegicus*) Wistar strain infected with *Staphylococcus aureus* infection based on serum amylase and lipase levels, and how the histopathology is. The sample in this study was male white rats (*Rattus norvegicus*) Wistar strain weighing 160-200gr and aged 2-3 months. Determination of the sample using the Ferderer formula for 4 groups and the overall results obtained were 24 rats which would be divided into 4 different groups. The first group as the control group, in this group the rats were only given distilled water. The treatment group was given Bacterial infection and clove extract with different doses, namely 200mg/KgBB, 400mg/KgBB, and 600mg/KgBB. *Staphylococcus aureus*is one type of pathogenic bacteria that often causes infections. The presence of *Staphylococcus aureus* in the bloodstream (bacteremia) can lead to the development of sepsis - a systemic inflammatory response to infection. A characteristic feature of sepsis is a paradoxical immunosuppressive response that sometimes occurs simultaneously with inflammation. This combination of inflammation and immunosuppression causes additional damage to local tissues and renders the body defenseless against pathogens and secondary infections. Staphylococcus can cause disease due to its ability to divide and spread widely into tissues through the production of several extracellular materials, one of which is the pancreas. The pancreas produces many enzymes, one of which is amylase and lipase. Amylase is a digestive enzyme that is mostly secreted by the pancreas and salivary glands and is found in other tissues in minimal amounts. Amylase was first described in the early 1800s and is one of the pioneer enzymes studied scientifically. Although this enzyme was originally called diastase, it was later renamed "amylase" in the early 20th century (Akinfemiwa et al., 2023). Damage to the pancreas will disrupt the human digestive system, therefore treatment is needed for bacterial infections in the form of plants that are rich in antioxidants and can be antibacterial agents. One of them is the clove plant. Syzygium aromaticum. Cloves contain non-volatile bioactive substances such as sterols, flavonoids, galloyl tannins, phenolic acids and triterpenes (Nikousaleg et al., 2016). Previous studies have shown that eugenol is the main component of clove extract which has antibacterial activity (Hariyadi, 2020). The results of phytochemical tests in this study showed that clove extract contains secondary metabolites in the form of flavonoids, saponins, tannins, and steroids. This research procedure was conducted for 14 days and produced data that

needed to be processed and tested first, so it was necessary to do some data analysis in the form of normality, homogeneity, and significance tests. The normality test data was obtained with the help of SPSS using the Kolmogorov-smirnov test. The results showed that the data for each group was normally distributed with a significance value of 0.200 in all test groups for testing serum lipase and amylase levels. So it can be concluded that the data is normally distributed, or can represent the population. The serum lipase and amylase levels were then tested for homogeneity using the Levene test to determine whether the data came from a population with the same variance. The results obtained showed a significance value of 0.694 for lipase levels and 0.526 for amylase levels. The probability value of significance obtained was greater than 0.05, so it can be concluded that the results of observations of serum lipase and amylase levels in the control group, treatment group 1, treatment group 2, and treatment group 3 were homogeneous or came from the same population. The normally distributed and homogeneous data were then tested for effectiveness and significance using the One-Way Anova test. The results of the One-way Anova test on the results of observations of serum lipase and amylase levels showed a significance value of 0.000 or greater than 0.05. Based on these data, it can be concluded that there is a significant difference between the control group, treatment group 1, treatment group 2, and treatment group 3 so that a further post-hoc LSD test is needed. The Post-hoc LSD test was conducted to analyze the differences in the average lipase and amylase between groups. The results of the analysis of serum lipase levels using the LSD Post Hoc Test were used to determine whether the group had a significant difference with other groups. The results of the analysis showed that there was a significant difference between the control group and treatment group 1 ($p = 0.000$) and treatment group 2 ($p = 0.000$). There was no significant difference between the control group and treatment group 3 ($p = 0.475$). The results of the analysis of serum amylase levels using the LSD Post Hoc Test were used to determine whether the group had a significant difference in amylase compared to other groups. The results of the analysis showed that there was a significant difference between the control group and treatment group 1 ($p = 0.000$). The control group and treatment group 2 obtained a significance value of 0.045. While the control group and treatment group 3 did not have a significant difference with a significance value of 0.821. Microscopic observation of histopathological images of pancreatic tissue was also carried out as additional research data. The control group had normal pancreatic histology. The results of this study indicate that administration of clove extract at doses of 400mg/KgBW and 600mg/KgBW can improve the histological structure of the pancreas in male white rats (*Rattus norvegicus*) of the Wistar strain that were infected. However, the dose of 600mg/KgBW is closer to the normal group. This can be seen from the results of histopathological observations of the pancreas in the control group and treatment group 3 which have shapes that are not much different.

Improvement of the histological structure of the pancreas of obese male white rats (*Rattus norvegicus*) of the Wistar strain cannot be separated from the content of compounds in the clove extract flower extract. Clove extract at a dose of 600mg/KgBW has secondary metabolite content that can repair damaged cell tissue due to bacterial infection and obesity conditions experienced by white rats (*Rattus norvegicus*) of the Wistar strain. Based on the results of histopathological observations on pancreatic tissue, researchers concluded that clove extract with doses of 400 mg/KgBB and 600 mg/KgBB can improve the histological structure of the pancreas in male white rats (*Rattus norvegicus*) of the Wistar strain that experienced infection. However, the dose of 600mg/KgBB is closer to the normal group. This can be seen from the results of histopathological observations of the pancreas in the control group and treatment group 3 which have shapes that are not much different. Improvement in the histological structure of the pancreas of male white rats (*Rattus norvegicus*) of the Wistar strain that experienced infection cannot be separated from the content of compounds in clove extract. Clove extract with a dose of 600mg/KgBB has secondary metabolite content that can repair damaged cell tissue due to bacterial infection and obesity conditions experienced by white rats (*Rattus norvegicus*) of the Wistar strain. The results of this study are in line with previous studies which found that clove extract showed the best inhibitory effect on bacterial infections. The proliferation of Staphylococcus simulans 2 was significantly inhibited without a logarithmic phase after clove extract treatment (Xu et al., 2023).

CONCLUSION

1. Clove extract contains secondary metabolites in the form of saponins, tannins, flavonoids and triterpenoids which help repair pancreatic cells damaged by *Staphylococcus aureus* infection.
2. Administration of clove extract at a dose of 600 mg/kgBW is effective in improving pancreatic function in white rats (*Rattus norvegicus*) Wistar strain that experience *Staphylococcus aureus* infection.
3. The results of histopathological observations of pancreatic tissue in treatment group 3 (600mg/KgBW) experienced the most significant improvement and approached the control group (reference group) compared to the other groups.

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