

# THE EFFECT OF GARLIC (*ALLIUM SATIVUM LINN*) SKIN EXTRACT ON NITRIC OXIDE AND TNF- $\alpha$ LEVELS IN ACUTE BACTERIAL SINUSITIS

Renny Swasti Wijayanti, Shelly Tjahyadewi, Isnawati Budi Panuntun Afifah

Otorhinolaryngology Department of Faculty of Medicine Sultan Agung Islamic University

Email: rennysw@gmail.com

---

**Keywords:**

Acute bacterial rhinosinusitis, Garlic (*Allium sativum* Linn) skin extract, Nitric oxide, TNF- $\alpha$

**ABSTRACT**

**Background :** During the course of the disease, acute bacterial rhinosinusitis produces several inflammatory mediators such as levels of Nitric Oxide (NO) and TNF- $\alpha$  which cause changes in cell and tissue structure. Currently, there is no research on the effect of garlic skin extract on nitric oxide and TNF- $\alpha$  levels in acute bacterial rhinosinusitis. **Methods :** This post-test only control group design experimental study used 28 male white rats of the Sprague Dawley strain which were divided into 4 groups, namely a control group, a group of rats with bacterial acute sinusitis without treatment, a group of rats with acute bacterial sinusitis with amoxicillin antibiotics and anti-inflammatory prednisolone, and a group Bacterial acute sinusitis rats with the antibiotic amoxicillin and garlic skin extract. The study was conducted for 21 days, on the 22nd day blood samples were taken from the orbital vein and measured levels of NO and TNF-  $\alpha$  using an ELISA reader. **Results :** The mean levels of TNF-  $\alpha$  in the first to fourth groups respectively were  $6.13 \pm 0.31$  ng/mL;  $17.68 \pm 4.29$  ng/mL ;  $6.65 \pm 0.43$  ng/mL ;  $6.86 \pm 0.26$  ng/mL. The analysis showed that the data were normally distributed and not homogeneous. The One Way ANOVA test showed that there were at least two groups of data that had a significant mean difference ( $p < 0.05$ ). The results of the LSD Post Hoc Test showed a significant difference between group K against P1, P2 and P3, group P1 against P2 and P3. And there was no significant difference between the P2 and P3 groups ( $p < 0.05$ ). **Conclusion :** The administration of garlic skin extract (*Allium sativum* Linn) affected the levels of NO and TNF- in rats with acute bacterial sinusitis induced by *Staphylococcus aureus*.

---

## INTRODUCTION

Rhinosinusitis is a disease that attacks the paranasal sinus mucosa involving inflammatory mechanisms. Rhinosinusitis is often identified with concomitant disease or carrier rhinitis, an inflammatory disease of the nasal mucosa so it is often called rhinosinusitis (Soepardi, 2011). It can be said that rhinosinusitis is acute if there are two or more symptoms suddenly, either stuffy nose, congestion, or nasal discharge accompanied by pain in the face or loss of smell for less than 4 weeks. Based on its cause acute rhinosinusitis is grouped into virus acute rhinosinusitis, post virus acute rhinosinusitis, and bacterial acute rhinosinusitis (Fokkens et al., 2020).

The main causes of inflammation of rhinosinusitis are viruses and bacteria (Karlsson, Shakeel, Supriya, Ram, & Ah-See, 2015). When the causative agent of rhinosinusitis invades the paranasal sinuses, there will be an inflammatory process that will invite various inflammatory mediators, one of which is TNF- $\alpha$ . In acute rhinosinusitis, TNF- $\alpha$  levels will increase. TNF- $\alpha$  is one of the many inflammatory mediators whose levels will increase in the acute inflammatory response to bacteria, viruses, fungi, and trauma. TNF- $\alpha$  levels will indicate how severe the degree of inflammation is (Anggraeni & Akbar, 2018). The inflammatory activity of rhinosinusitis can also be affected by nitric oxide (NO). NO is an inflammatory free radical, where NO is produced by L-arginine assisted by nitric oxide synthase (NOS). NOS differentiated into inducible Nitric Oxide synthase (iNOS) plays a role in the regulation and enhancement of cyclooxygenase-2 (COX-2) and affects the inflammatory process (Anggraeni & Akbar, 2018)

The prevalence of acute sinusitis is increasing. Cases of sinusitis are reported to occur between 1% to 12% of all cases of the disease worldwide (Xu et al., 2016). In the United States, there are approximately 14.7% of sinusitis cases in adults each year (Rosenfeld et al., 2015). Sinusitis is also one of the most common reasons patients come to the doctor. The health budget for sinusitis cases costs nearly \$2.4 billion annually and approximately 200.000 American people undergo sinusitis surgery annually (Vrontis, Christofi, Battisti, & Graziano, 2021). The prevalence of sinusitis cases in Indonesia is still quite high. According to data from the Indonesian Ministry of Health (2013), sinusitis got the order 25 of the 50 most common causes of the disease in Indonesia or about 102.817 patients in various health facilities, according to the results of observations carried out by the ENT section of RSCM in January to August 2016 obtained the number of sinusitis patients is 435 patients (69%) (Nurmalasari & Nuryanti, 2017). Therefore, sinusitis is one of the causes of diseases that have a high economic burden and a considerable decrease in quality of life, decreased productivity, and also concentration in work (Harahap, 2018).

Inflammation is a series of forms of protection of the body against foreign bodies and tissue damage (Bao, Sherwood, & Sun, 2018). In the process of the course of the disease, sinusitis produces several inflammatory mediators that cause changes in the structure of cells and tissues. Inflammatory mediators that will appear when the sinusitis inflammatory process occurs, namely; Interferon (IFN), Colony-Stimulating Factors (CSF), Interleukin (IL), and Tumor Necrosis Factors (TNF). TNF- $\alpha$  is one of the inflammatory mediators that plays a big role in the inflammatory process

and will cause a variety of clinical manifestations (Quintana, Bilbao, Comas-Barceló, Bujons, & Triola, 2019). The inflammatory activity of sinusitis can also be affected by nitric oxide (NO). NO is an inflammatory free radical, where NO is produced by L-arginine assisted by nitric oxide synthase (NOS). NOS differentiated into inducible Nitric Oxide synthase (iNOS) plays a role in the regulation and enhancement of cyclooxygenase-2 (COX-2) and affects the inflammatory process. Flavonoids such as quercetin can inhibit the formation of iNOS and prevent excess NO production (Pakrashi et al., 2014).

Garlic is one of the spice plants that are very abundant in Indonesia. Generally, this plant is only used as a flavoring agent for food and traditional herbal medicine that can treat various diseases. Garlic skin that has only ended up as garbage or waste turns out to have content that is no less useful than the tubers. A study conducted by (Febrinasari, Wijayanti, & Apriadi, 2016) showed that the skin of garlic (*Allium sativum* Linn) contains flavonoid compounds that act as anti-inflammatories. Other studies showed that flavonoid compounds owned by garlic peel (*Allium sativum* Linn) will prevent the release of TNF- $\alpha$  and NO to relieve inflammation (Abd El-Hack et al., 2020).

#### RESEARCH METHODS

The research conducted includes a type of experimental research using a "post-test only controlled group design" research design. Experimental research will look at the effect of garlic skin extract (*Allium sativum* Linn) on levels of NO and TNF- $\alpha$  male white rat *Rattus Copernicus* strain Sprague Dawley exposed by *Staphylococcus aureus*. The research was conducted at the Nutrition Laboratory of the Center for Food and Nutrition Studies (PSPG) Gadjah Mada Yogyakarta University from August 2021 to September 2021. The study used samples of male Sprague Dawley strain rats kept at the Nutrition Laboratory of the Center for Food and Nutrition Studies (PSPG) Gadjah Mada University. The study sample involved 28 rats. The sample size in this study was 6 rats for each group that had been randomized. This study, used 4 treatment groups so that the animals were tested and overstated by 10% (1 rat) to overcome the dropout. Sampling is carried out according to inclusion and exclusion criteria until the minimum sample amount is met. Data collection is obtained by calculating NO and TNF- $\alpha$  levels using the ELISA method from all research test subjects. The data obtained is then conducted a descriptive test to find out the average value and standard deviation. The normality test uses Shapiro-Wilk and the group homogeneity test uses Levene's Test. Using SPSS app version 22.

#### RESULTS AND DISCUSSION

The group that received a combination treatment of garlic peel extract with amoxicillin had slightly higher levels of TNF- $\alpha$  ( $6.86 \pm 0.26$  ng/mL) than the group that received a combination treatment of prednisolone with amoxicillin ( $6.65 \pm 0.43$  ng/mL).

#### Table 1 Overview of Average TNF- $\alpha$ levels (ng/mL)

Group	Average ± SD
K	6,13 ± 0,31
P1	17,68 ± 4,29
P2	6,65 ± 0,43
P3	6,86 ± 0,26

Description : K = standard feed diet (control), P1 = Staphylococcus aureus induction, P2 = Staphylococcus aureus induction + amoxicillin + prednisolone, P3 = Staphylococcus aureus induction + amoxicillin + garlic skin extract

The results of the normality test using the Shapiro-Wilk method (due to the large sample in this study  $\leq 30$ ) found that all groups had normal distribution data ( $p > 0.05$ ). The data was also conducted homogeneity test, namely Levene's test obtained non-homogeneous data ( $p = 0.381$ ).

The one way ANOVA test showed the value of  $p = <0.001$  ( $p < 0.05$ ) so from the results it can be concluded that there are at least 2 groups that have significant differences. Post-Hoc LSD tests were conducted to find out which groups had significant differences. The results of the Post-Hoc LSD test are displayed in table 4.2.

**Table 2 Lsd Post-Hoc Test Results**

Group	K	P1	P2	P3
K	–	<0,001	0,024	0,002
P1	<0,001	–	<0,001	<0,001
P2	0,024	<0,001	–	0,317
P3	0,002	<0,001	0,317	–

Description : K = standard feed diet (control), P1 = Staphylococcus aureus induction, P2 = Staphylococcus aureus induction + amoxicillin + prednisolone, P3 = Staphylococcus aureus induction + amoxicillin + garlic skin extract

The results of the Post-Hoc LSD test showed that between the control group of P1, P2, and P3, the P1 group against P2 and P3 obtained a  $p < 0,05$ , so it can be concluded that there is a significant difference. While between P2 to P3 the value of  $p > 0.05$  or insignificant.

The group that received a combination treatment of garlic skin extract with amoxicillin had higher LEVELS of NO ( $27.82 \pm 0.44$  ng/mL) than the group that

received a combination treatment of prednisolone with amoxicillin ( $27.28 \pm 0.87$  ng/mL). This can be seen in table 4.3.

**Table 3 Average Picture of NO levels (ng/mL)**

Group	Average $\pm$ SD
K	26,20 $\pm$ 0,63
P1	77,89 $\pm$ 8,53
P2	27,28 $\pm$ 0,87
P3	27,82 $\pm$ 0,44

The results of the normality test using the Shapiro-Wilk method (due to the large sample in this study  $\leq 30$ ) found that all groups had normal distribution data ( $p > 0,05$ ). The data was also conducted homogeneity test, namely Levene's test obtained non-homogeneous data ( $p = 0,381$ ).

The one-way ANOVA test showed that the 2 groups had significant differences with p values  $< 0,05$ . The Post-Hoc Games-Howell test was conducted to find out which groups had significant differences. Post-Hoc Games-Howell test results are displayed in table 4.4.

**Table 4 Games-Howell Post-Hoc Test Results**

Group	K	P1	P2	P3
K	–	$<0,001^*$	0,130	0,003
P1	$<0,001^*$	–	$<0,001^*$	$<0,001^*$
P2	0,130	$<0,001^*$	–	0,317
P3	0,003	$<0,001^*$	0,555	–

Description: K = standard feed diet (control), P1 = induction staphylococcus aureus, P2 = induction Staphylococcus aureus + amoxicillin + prednisolone, P3 = induction Staphylococcus aureus + amoxicillin + garlic skin extract

\* = normal distributed ( $p > 0,05$ )

The results of the Post-Hoc Games-Howell test showed that between the control group against P1, P2, and P3, the P1 group against P2 and P3 obtained a p value

of  $< 0,05$ , so it can be concluded that there is a significant difference. While between K to P2 and P2 against P3 p value  $> 0.05$  or insignificant.

The inflammatory activity of sinusitis that occurs in the sinonasal mucosa is affected by the NO produced by L-arginine assisted nitric oxide synthase (NOS) and differentiated into inducible Nitric Oxide synthase (iNOS) which plays a role in the increase of cyclooxygenase-2 (COX-2) and affects the inflammatory process, whereby iNOS will be expressed when macrophages are activated by pro-inflammatory cytokines such as IFN- $\gamma$ , and induce the production of NO (Kumar, Abbas and Aster, 2018).

From the results of the Anova test, the value of  $p = < 0.001$  and the Levene test value  $p = < 0.001$  because the value of  $p < 0.05$  and Levene  $< 0.05$  so from the results it can be concluded that there are significant differences in the four treatment groups with different data variants and showed that there were at least 2 groups that had a meaningful difference in average NO levels which meant there was an influence of amoxicillin and garlic skin extract (*Allium Sativum* Linn) on NO levels. NO levels were lower ( $26.20 \pm 0.63$ ) than the induction group staphylococcus aureus ( $77.89 \pm 8.53$  ng/mL). The increase in the staphylococcus aureus induction group is due to exposure to pathogens that activate T lymphocyte cells to release IFN- $\gamma$  and activate macrophage cells to synthesize i-NOS. i-NOS formed will occur catalysis reaction L-arginine to NO and L-citrulline. NO is released then out of macrophage cells and there is an increase in NO levels during the inflammatory process (Kumar, Abbas, and Aster, 2018). This is in line with research conducted by Tjahjani (2016) where induction of staphylococcus aureus triggered an increase in NO levels in the positive K group compared to the negative K group (Tjahjani, Kristina, and Lestari, 2016). Like other gram-positive bacteria, staphylococcus aureus has a quorum-sensing system in which bacteria can communicate with each other in regulating biofilm maturation, regulation of bacterial gene expression, virulence, and colonization. So that the increased colonization of *s. aureus* triggers the NO-mediated innate defense pathway in the epithelium of the upper airway as well as the product results of *s. aureus* can increase the formation of NO (Carey, 2015).

The results of this study in the Anova test obtained a value of  $p = < 0.001$  ( $p < 0.05$ ) showing that there were at least 2 groups that had significant differences. In the control group, TNF- $\alpha$  had lower levels ( $6.13 \pm 0.31$  ng/mL) than the Staphylococcus aureus induced group ( $17.68 \pm 4.29$  ng/mL). The increase in the Staphylococcus aureus induction group is due to bacterial exposure to stimulating phagocytosis, activating T cells, and activating macrophages to produce TNF- $\alpha$ . IFN- $\gamma$  produced by T cells and NK cells also stimulates the synthesis of TNF- $\alpha$ . This is in line with research conducted by Tjahjani et al. (2016) where induction of Staphylococcus aureus can stimulate increased levels of TNF- $\alpha$  in positive K groups compared to negative K groups (Tjahjani, Kristina, and Lestari, 2016).

In the Staphylococcus aureus induction group, higher levels of NO ( $77.89 \pm 8.53$  ng/mL) were seen compared to the treatment group of amoxicillin and garlic skin extract ( $27.82 \pm 0.44$  ng/mL) with a  $p < 0.001$ . This means that the combination of garlic skin extract with amoxicillin effectively lowers NO levels in

acute sinusitis rat. These results are in line with a study by Sholikhah and Rahayuningsih (2015) that used the active ingredients of lompong extract, showing that flavonoids in lompong plant extracts have anti-inflammatory effects shown by decreased NO levels through an increased mechanism of phagocytosis by macrophages, thereby preventing inflammation from becoming chronic (Sholikhah and Rahayuningsih, 2015). Garlic skin extract contains the active compounds of alkaloid, quinone, saponin, and flavonoid. Flavonoid are anti-inflammatory by inhibiting lipopolysaccharide-induced NO release (LPS) by suppressing LPS-induced expression of iNOS proteins and affecting the work of M1 macrophages in iNOS synthesis with a decrease of about 98% (Cho et al., 2013). The antibiotic amoxicillin of the main therapy for sinusitis can lower NO levels through a bactericidal process that causes lysis of the cell wall, thereby destroying bacterial cells and the number of bacteria is reduced. A decrease in the number of bacteria affects the release of iNOS by macrophages that are reduced so that NO levels fall (Schairer et al., 2012).

The group that received a combination of amoxicillin and garlic peel extract ( $6.86 \pm 0.26$  ng/mL) had lower levels of TNF- $\alpha$  than the *Staphylococcus aureus* induced group without being given therapy ( $17.68 \pm 4.29$  ng/mL). The results of the analysis showed that the average difference between the two groups was statistically significant ( $p < 0.001$ ) which meant there was a significant difference between the *staphylococcus aureus* induced rat groups without being given therapy with the group that received a combination treatment of amoxicillin with garlic skin extract. This means that the combination of garlic skin extract with amoxicillin effectively lowers TNF- $\alpha$  levels in bacterial acute sinusitis rat. The results are in line with the research of Moutia et al. (2018) who used garlic extract in their research which is known to improve the regulation of IL-10 which acts as negative feedback in signaling pro-inflammatory responses by inhibiting the production of TNF- $\alpha$  and IL-6 pro-inflammatory cytokines (Moutia, Habti, and Badou, 2018). Research using other active ingredients, namely binahong leaf extract and garlic extract, also showed that the combination of binahong leaf extract and garlic extract had a significant influence on inflammation (Deswati et al., 2020). Allicin compound in garlic skin have also been shown to reduce macrophage production by suppressing phosphatase activity. Declining macrophages will affect TNF- $\alpha$  whose production is sourced from macrophages. Garlic skin also has a variety of chemical compounds that are identical to chemical compounds in garlic, such as saponin, alkaloid, flavonoid, quinone, and allicin that can act as anti-inflammatories (Wijayanti and Rosyid, 2015).

The amoxicillin treatment group with garlic skin had higher average NO levels ( $27.82 \pm 0.44$  ng/mL) than the group that received a combination treatment of amoxicillin with prednisolone ( $27.28 \pm 0.87$  ng/mL). The results of the analysis showed a value of  $p = 0.555$  which means that there is no difference between the administration of garlic skin extract and prednisolone in lowering NO levels. Research conducted by Mohammed et al., 2014 is on the inflammatory process, the content of garlic skin compounds that play a role is a flavonoid. Flavonoids are polyphenol compounds that have the ability in the inflammatory process, especially in the inflammatory and proliferation phases of wound healing or tissue damage where

flavonoids will suppress the production of pro inflammatory mediators (IL-6, TNF- $\alpha$ , and NO) by macrophage M1 (Mohammed et al., 2014). M1 macrophages are macrophages that induce the enzyme iNOS so that NO production increases, especially in damaged body tissues (Ley, 2017). In a study conducted by Luan and Chen, 2017, glucocorticoids can prevent inflammation by down-regulating GR- $\beta$  expression in salpingitis. GR- $\beta$  is a glucocorticoid receptor that plays a role in pathological conditions such as inflammation, while GR- $\alpha$  is a classic glucocorticoid receptor that plays a role in the mediation of glucocorticoid activity. Staphylococcus aureus infection will increase GR- $\beta$  and lower GR- $\alpha$  levels, glucocorticoid interventions restrain GR- $\beta$  expression so that inflammatory mediators in salpingitis are disrupted and will affect NO levels (Luan and Chen, 2017). One of the effects of the decrease in NO levels is giving the amoxicillin antibiotics which are a beta-lactam antimicrobial group. Beta-lactam works by attaching to penicillin-binding protein that inhibit a process called transpeptidation which is a cross binding process in cell wall synthesis leading to the activation of autolytic enzymes in bacterial cell walls. This process causes the lysis of the cell wall, thereby destroying bacterial cells (Bernatová et al., 2013). The decreased number of bacteria due to bactericidal processes by amoxicillin also decreases the release of iNOS by macrophages so that NO synthesis can be reduced (Schairer et al., 2012).

The group that received a combination treatment of garlic skin extract with amoxicillin had higher levels of TNF- $\alpha$  ( $6.86 \pm 0.26$  ng/mL) than the group that received a combination treatment of prednisolone with amoxicillin ( $6.65 \pm 0.43$  ng/mL). The results of the statistical analysis showed a value of  $p = 0.371$  which means that there is no meaningful difference between giving of garlic skin extract and prednisolone in lowering TNF- $\alpha$  levels.

It can be interpreted that garlic skin extract has the same effect compared to prednisolone in lowering TNF- $\alpha$  levels in bacterial acute sinusitis rat. This is in line with research conducted by Venekamp et al. (2014) on prednisolone interventions in sinusitis, where the corticosteroid class medicine prednisolone can inhibit the transcription of pro-inflammatory mediators including TNF- $\alpha$  in human airway endothelial cells and potentially act as anti-inflammatory and decongestant agents (Venekamp et al., 2014). Fernandes and McKay's research (2013) also showed that prednisolone would work as a dominant anti-inflammatory mediated by inhibition of prostaglandin synthesis through two actions on the arachidonic acid pathway. First, prednisolone inhibits specific transcription factors, AP-1 and NF- $\kappa$ B, which are involved in the regulation of pro-inflammatory protein, including induced cyclooxygenase-2. Second, prednisolone will stimulate the production of the anti-inflammatory protein annexin-1, which has the effect of inhibiting phospholipase A2 – a speed-limiting enzyme involved in the synthesis of arachidonic acid (Fernandes and McKay, 2013). Research conducted by Rodrigues and Percival (2019) explains that organosulfur compounds derived from garlic (including flavonoid, allicin, etc.) have the potential to stimulate the production of hydrogen sulfide (H<sub>2</sub>S) which will reduce the expression of proinflammatory cytokines. This can occur due to the suppression



of  $\text{nf-}\kappa\text{B}$  transcription factors and the reduction of mRNA expression of  $\text{TNF-}\alpha$ ,  $\text{IFN-}\gamma$ ,  $\text{IL-1}\beta$ ,  $\text{IL-2}$ , and  $\text{IL-12}$  (Rodrigues and Percival, 2019).

This study is the first to investigate the effect of garlic skin extract on NO and  $\text{TNF-}\alpha$  levels in acute sinusitis rat. This is the main advantage of this study because of the value of novelty (novelty). This study has some limitations. First, the study did not examine the dominant active ingredients acting as anti-inflammatories in the reduction of NO and  $\text{TNF-}\alpha$  levels. Second, this study used only one dose so researchers could not see the effect of the difference that occurred if given on multiple doses.

## CONCLUSION

- a. Giving of the antibiotic amoxicillin 27 mg/day and garlic skin extract 756mg / 200gBB / day affected the levels of NO and  $\text{TNF-}\alpha$  acute sinusitis rat induced *Staphylococcus aureus*.
- b. Average nitrite oxide levels in male white rat Sprague Dawley strain the only standard feed is  $26.20 \pm 0.63$  ng/mL.
- c. The average level of  $\text{TNF-}\alpha$  in male white rat of the Sprague Dawley strain which was only given standard feed was  $6.13 \pm 0.31$  pg / mL.
- d. The average nitrite oxide levels in male white rat of the Sprague Dawley strain that induced *Staphylococcus aureus* without treatment were  $77.88 \pm 8.53$  ng/mL.
- e. The average  $\text{TNF-}\alpha$  level in male white rat of the Sprague Dawley strain that induced *Staphylococcus aureus* without treatment was  $17.68 \pm 4.29$  pg/mL.
- f. The average nitrite oxide level in male white rat of the Sprague Dawley strain that induced *Staphylococcus aureus* and giving of the antibiotic amoxicillin 27 mg/day + prednisolone 0.54 mg/day was  $27.28 \pm 0.87$  ng/mL.
- g. The average levels of  $\text{TNF-}\alpha$  in male white rat of the Sprague Dawley strain that induced *Staphylococcus aureus* and giving of amoxicillin antibiotics 27 mg/day + prednisolone 0.54 mg/day were  $6.65 \pm 0.43$  pg/mL.
- h. The average nitrite oxide levels in male white rat of the Sprague Dawley strain that induced *Staphylococcus aureus* and given garlic skin extract 756mg/200gBB/day + amoxicillin antibiotic 27 mg/day was  $27.82 \pm 0.44$  ng/mL.
- i. The average levels of  $\text{TNF-}\alpha$  in male rat of the Sprague Dawley strain that induced *Staphylococcus aureus* and given garlic skin extract 756mg/200gBB/day + amoxicillin antibiotic 27 mg/day was  $6.86 \pm 0.26$  pg/mL.

## REFERENCES

- Anggraeni, D. dan Kamaluddin, H. M. T. (2018) 'Efektivitas Gel Ekstrak Air Bawang Putih (*Allium sativum*. L) Terhadap Kadar Tumor Necrotic Factor Alfa ( $\text{TNF-}\alpha$ ) Dan Diameter Ulkus Mulut Pada Tikus Putih Jantan Galur Wistar', Efektivitas Gel Ekstrak Air Bawang Putih (*Allium sativum*. L) Terhadap Kadar

Tumor Necrotic Factor Alfa (TNF- $\alpha$ ) Dan Diameter Ulkus Mulut Pada Tikus Putih Jantan Galur Wistar, 4(3), pp. 128–139.

Batiha, E.-S. et al. (2020) 'Chemical Constituents and Pharmacological', *Nutrients*, 12(3), p. 872.

Battisti, A. S., Modi, P. dan Pangia, J. (2020) Sinusitis. StatPearls Publishing, Treasure Island (FL). Available at: <http://europepmc.org/books/NBK470383>.

Deswati, D. A. et al. (2020) 'Uji Efek Anti Inflamasi Kombinasi Ekstrak Daun Binahong Dan Ekstrak Bawang Putih Terhadap Tikus Jantan Galur Wistar', *Jurnal Sabdariffarma*, 2(2), pp. 21–27. Available at: <https://journal2.unfari.ac.id/index.php/sabdariffarma/article/view/115>.

Fernandes, S. dan Mckay, G. (2013) 'Prednisolone (Drug Notes) - Practical Diabetes', 30(6), pp. 251–253.

Fokkens, W. J. et al. (2020) 'European Position Paper on Rhinosinusitis and Nasal Polyps 2020', *Official Journal of the European and International Rhinologic Societies and of the Confederation of European ORL-HNS*, Suppl 29, pp. 1–464.

Ley, K. (2017) 'M1 Means Kill; M2 Means Heal', *The Journal of Immunology*, 199(7), pp. 2191–2193. doi: 10.4049/jimmunol.1701135.

Luan, S. X. and Chen, X. H. (2017) 'The glucocorticoid inhibits neutrophils formed extracellular traps (NETs) and suppresses the inflammation caused by fallopian tube staphylococcal infection', *European review for medical and pharmacological sciences*, 21(4), pp. 855–860.

Mohammed, M. S. et al. (2014) 'Secondary metabolites as anti-inflammatory agents', *The Journal of Phytopharmacology*, 3(4), pp. 275–285.

Nurmalasari, Y. and Nuryanti, D. (2017) 'Faktor-Faktor Prognostik Kesembuhan Pengobatan Medikamentosa Rinosinusitis Kronis Di Poli THT RSUD A. Dadi Tjokrodipo Bandar Lampung Tahun 2017', *Jurnal Ilmu Kedokteran dan Kesehatan*, 3(4), pp. 188–197.

Moutia, M., Habti, N. dan Badou, A. (2018) 'In Vitro and In Vivo Immunomodulator Activities of *Allium sativum* L.', *Evidence-based Complementary and Alternative Medicine*. doi: 10.1155/2018/4984659.

Nurmalasari, Y. dan Nuryanti, D. (2017) 'Faktor-Faktor Prognostik Kesembuhan Pengobatan Medikamentosa Rinosinusitis Kronis Di Poli THT RSUD A. Dadi Tjokrodipo Bandar Lampung Tahun 2017', 3(April), pp. 188–197.

- Rodrigues, C. dan Percival, S. S. (2019) 'Immunomodulatory effects of glutathione, garlic derivatives, and hydrogen sulfide', *Nutrients*. doi: 10.3390/nu11020295.
- Sherwood, L. (2018) *Human Physiology : From Cells to Systems*. 9th edn. Edited by J. Suyono et al. Jakarta: Penerbit Buku Kedokteran EGC.
- Tjahjani, N. P., Kristina, T. N. dan Lestari, E. S. (2016) 'Efektivitas ekstrak etanol daun ungu (*Gratophyllum pictum* (L.)) untuk menurunkan kadar TNF- $\alpha$  dan NO', *Pharmaciana*, 6(2). doi: 10.12928/pharmaciana.v6i2.3610.
- Triola, S. (2019) 'Pengaruh Cuci Hidung dengan NaCl 0,9% Terhadap Ekspresi Gen IL-1Beta dan TNF-Alpha Mukosa Hidung Penderita Rinosinusitis Kronis di RSUP Dr M Djamil Padang', *Health & Medical Journal*, 1(2), pp. 17–27. doi: 10.33854/heme.v1i2.236.
- Venekamp, R. P. et al. (2014) 'Systemic corticosteroids for acute sinusitis', *Cochrane Database of Systematic Reviews*, 2014(3). doi: 10.1002/14651858.CD008115.pub3.
- Wijayanti, R. dan Rosyid, A. (2015) 'Efek Ekstrak Kulit Umbi Bawang Putih (*Allium Sativum* L.) terhadap Penurunan Kadar Glukosa Darah pada Tikus Putih Jantan Galur Wistar yang Diinduksi Aloksan', pp. 47–52.
- Xu, Y. et al. (2016) 'Prevalence and incidence of diagnosed chronic rhinosinusitis in Alberta, Canada', *JAMA Otolaryngology - Head and Neck Surgery*, 142(11), pp. 1063–1069. doi: 10.1001/jamaoto.2016.2227.

---

**Copyright holder:**

Renny Swasti Wijayanti, Shelly Tjahyadewi, Isnawati Budi Panuntun  
Afifah Fairuz Zahira (2023)

First publication right:  
Jurnal Health Sains

This article is licensed under:

