ABSTRACT

Objective: This research aimed to show effect of black cumin (nigella sativa) on blood pressure, mean arterial pressure (MAP), proteinuria in preeclamptic model rats.

Methods: This is an analytical research with true experimental design in laboratory pregnant female rats (Rattus norvegicus), which get black cumin seed extract (Nigella sativa) at a dose of 500 mg/kg/day and 2000 mg/kg/day. The treatment was observed using Postest Only Control Group Design. The research was conducted at Biology Laboratory in July 2019. To assess the comparison of parameters (systolic and diastolic blood pressure, mean arterial pressure and proteinuria) between groups the ANOVA test was used if the data were normally distributed and Kruskal Wallis test was used if the data were abnormally distributed.

Results: Systolic and diastolic blood pressure and MAP decreased in preeclampsia models rats by administering 500 mg (P1) and 2000 mg (P2). However, a dose of 2000 mg black cumin extract had a more significant decrease in systolic blood pressure and MAP. The results of this research indicate that all treatment groups showed improvement after day 9 of the administration of nigella that no treatment group showed proteinuria.

Conclusion: Black cumin is proven to reduce systolic and diastolic blood pressure, Mean Arterial Pressure and proteinuria.

Keywords: Black cumin, Systolic, Diastolic, Mean arterial pressure, Proteinuria
This can be seen in fig. 1. In the group of rats given black cumin pressure during monitoring compared to the negative control group. In the positive control group, there was an increase in systolic blood pressure within the normal range obtained during monitoring. From fig. 1. it was found that blood pressure in treatment group 1 (P1) and group 2 (P2) showed a decrease in systole blood pressure. Systolic blood pressure decreased in preeclampsia models rats by administering black cumin extract with a dose of 500 mg (P1) and 2000 mg (P2). However, a dose of 2000 mg black cumin extract significantly decrease systolic blood pressure than 500 mg black cumin extract.

### Characteristics of experimental animals

#### Table 1: Trial distribution group

| Group                        | F   | %    |
|------------------------------|-----|------|
| Control-(C-)                 | 6   | 25.0 |
| Control+(C+)                 | 6   | 25.0 |
| Nigella Sativa 500 (T1)      | 6   | 25.0 |
| Nigella Sativa 2000 (T2)     | 6   | 25.0 |
| Total                        | 24  | 100.0|

Systolic and diastolic blood pressure after administration of black cumin extract (Nigella sativa) in preeclampsia model rats

From the results of this research, obtained systolic and diastolic blood pressure in the negative control group, positive control group, and the treatment group. Can be seen in the negative control group, blood pressure within the normal range obtained during monitoring. In the positive control group, there was an increase in systolic blood pressure during monitoring compared to the negative control group. This can be seen in fig. 1. In the group of rats given black cumin extract showed a decrease in systolic blood pressure. This indicates a change in systolic blood pressure in experimental animals.

From fig. 1. it was found that blood pressure in treatment group 1 (P1) and group 2 (P2) showed a decrease in systole blood pressure. Systolic blood pressure decreased in preeclampsia models rats by administering black cumin extract with a dose of 500 mg (P1) and 2000 mg (P2). However, a dose of 2000 mg black cumin extract significantly decrease systolic blood pressure than 500 mg black cumin extract.

**Fig. 1:** Administration of black cumin extract can reduce systolic blood pressure in the case group, whereas the positive control group still shows an increase in systolic blood pressure.
From the fig. below, it can be seen the diastole blood pressure values in the treatment group 1 (P1) at a dose of 500 mg and treatment group 2 (P2) at a dose of 2000 mg experienced a decrease approaching the diastole value in normal rat group.

Based on table 2, it was found that changes in blood pressure from the 1st day to the 15th day had a significant difference, where there was a significant difference in blood pressure values in the normal (C-) group and the preeclampsia (C+) group (p<0.000, CI 95%: 38.59-29.10); normal rat group with rat given 500 mg black cumin extract groups (p<0.000, CI 95%: 34.06-21.49); normal rat groups with rat given 2000 mg black cumin extract groups (p<0.000, CI 95%: 24.85-16.22). There was a significant difference in blood pressure in the rat with LPS injection group with a negative group (p<0.000, CI 95%: 29.10-37.17). There was a significant difference between the positive control group and rat given 500 mg black cumin extract group (p=0.058, CI 95%: 19-85.59); there was a significant difference between the positive control group and rat given 2000 mg black cumin extract group (p<0.000, CI 95%: 9.07-12.33). There was a significant difference in rat given 500 mg black cumin extract group with a positive control group (p<0.000, CI 95%: 21.49-34). There was a difference in blood pressure in the rat group with black cumin dose
2000 mg with negative control group (p<0.000, 95% CI-17.55-9.07); there was a difference in blood pressure in the rat given 2000 mg black cumin extract and 500 mg black cumin extract group (p = 0.022, 95% CI-13.38-1.09).

**Table 2: Comparison of mean values of blood pressure of mice**

| (I) klp | (J) klp | Mean difference (I-J) | Std. error | Sig. | 95% confidence Lower bound | Upper bound |
|---------|---------|-----------------------|------------|------|-----------------------------|-------------|
| C-      | C+      | -33.85*               | 1.455      | .000 | -38.59                     | -29.10      |
| T1      | 6.07    | 1.862                 | 0.000      | -34.06 | -21.49                     |
| T2      | -20.54* | 1.296                 | 0.00       | -24.85 | -16.22                     |
| C+      | C-      | 33.85*               | 1.455      | .000 | 29.10                      | 37.17       |
| T1      | 6.07    | 1.862                 | 0.000      | -19  | 38.59                      |
| T2      | 13.31*  | 1.276                 | 0.00       | 9.07  | 12.33                      |
| T1      | C+      | 27.77*               | 1.862      | .000 | 21.49                      | 34.06       |
| T2      | -6.07   | 1.849                 | 0.058      | -12.33 | 1.9                      |
| C+      | T1      | 20.54*               | 1.296      | .000 | 16.22                      | 24.85       |
| C-      | T2      | 13.31*               | 1.276      | .000 | 9.07  | 12.33                     |

**Comparison of mean arterial pressure (MAP) after black cumin extract administration**

Based on table 3, it was found that MAP change from the 1st day to the 15th day had a significant difference, where there were significant differences in blood pressure values in normal (C-) group and the preeclampsia (C+) group (p<0.001, CI 95%-46.35-37.48); normal rat group with rat given 500 mg black cumin extract groups (p<0.000, CI 95%-33.74-23.41); normal rat group with rat given 2000 mg black cumin extract groups (p<0.001, CI 95%-25.70-17.83). There was a significant difference in blood pressure in the rat given LPS injection group with rat given 500 mg black cumin extract groups (p<0.001, 95% CI 1.85-11.76); there was a significant difference between the positive control group and rat given 2000 mg black cumin extract group (p<0.001, CI 16.11-24.18); there was a significant difference between the positive control group and the negative control group (p<0.001, CI 23.4-33.74) There was a significant difference in rat given 500 mg black cumin extract group with a positive control group (p<0.001, 95% CI 18.55-8.12); there was a significant difference on blood pressure between rat given 500 mg black cumin extract groups and rat given 2000 mg black cumin extract group (p<0.001, 95% CI 1.85-11.76); there was a significant difference between rat given 500 mg black cumin extract groups and negative control group (p<0.001, 95% CI 17.83-25.70). There was a difference in blood pressure in the rat given 2000 mg black cumin extract group with positive control group (p<0.001, CI 95%-24.18-16.11).

**Table 3: Comparison of mean arterial pressure (MAP) value in model mice**

| (I) klp | (J) klp | Mean difference (I-J) | Std. error | Sig. | 95% confidence Lower bound | Upper bound |
|---------|---------|-----------------------|------------|------|-----------------------------|-------------|
| C-      | C+      | -41.92                | 1.35       | <0.0001 | -46.35                      | -37.48      |
| T1      | 28.57   | 1.57                  | <0.0001    | -33.74 | -23.41                      |
| T2      | 21.76   | 1.18                  | <0.0001    | -25.70 | -17.83                      |
| C+      | C-      | 41.92                | 1.35       | <0.0001 | 37.48                      | 46.35       |
| T1      | 13.34   | 1.57                  | <0.0001    | 8.12  | 18.55                      |
| T2      | 20.15   | 1.21                  | <0.0001    | 16.11 | 24.18                      |
| T1      | C+      | 28.57                | 1.55       | <0.0001 | 23.4                      | 33.74       |
| C+      | T1      | 12.34                | 1.57       | <0.0001 | -18.55                     | -8.12       |
| C-      | T2      | 6.80                 | 1.43       | <0.0001 | 1.85                       | 11.76       |
| T2      | 21.76   | 1.18                  | <0.0001    | 17.83 | 25.70                      |
| C+      | C-      | 20.15                | 1.21       | <0.0001 | -24.18                     | -16.11      |
| T1      | -6.81   | 1.43                  | <0.0001    | -11.76 | -1.85                      |
From the image below it can be seen the mean MAP comparison in each group of rats. This results showed MAP decrease in rat given 500 mg and 2000 mg black cumin extract. However, a more significant decrease in MAP was seen in rat given 2000 mg black cumin extract.

Comparison of proteinuria in each study group

In fig. 6, Proteinuria shows a decrease per day where it appears the role of black cumin can reduce protein in the urine.

Table 4: Proteinuria in the study group from day 1 to day 15

| Proteinuria | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 |
|-------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| C -         | 6  | 1  | 6  | 10 | 6  | 10 | 6  | 10 | 6  | 10 | 6  | 10 | 6  | 10 | 6  | 10 |
| +           | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| + 1         | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| + 2         | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| + 3         | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| T -         | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| +           | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| + 1         | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| + 2         | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| + 3         | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| T -         | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |

DISCUSSION

Changes of mean systole in preeclampsia by administration of black cumin extract (Nigella sativa)

The results of this study are in line with the study of Jarin et al., 2015 in which the administration of a combination of black cumin extract (Nigella Sativa) and nicardipine showed a significant decrease in systolic blood pressure. A decrease in systolic blood pressure with Nigella sativa was also followed by a significant decrease in MDA, ACE, NADPH oxidase activity and increased activity of HO-1 in cardiac, which was also accompanied by an increase in plasma NO [13].
The antioxidant effect of Nigella Sativa is also often reported lately. Antioxidant effect of Nigella Sativa which contributes to the antihypertensive effect. Apart from its antioxidant activity, the blood pressure reduction effect of Nigella Sativa can be caused by antidiuretic, anti-inflammatory, or protective effects on the kidneys [14, 15].

Endothelium has an important role in vascular muscle relaxation, where several studies have confirmed the involvement of the role of blood vessels as part of the pathophysiology of hypertension [16]. Nigella Sativa extract dose of 30 mg/ml can produce vasorelaxant effects of blood vessels. Thus, Nigella Sativa extract works the same as a blood vessel relaxant factor (Nitrite oxidant or prostacyclin) which causes vasodilatation [17].

Previous studies also reported that essential oils from black cumin and thymoquinone lowered blood pressure and heart rate, both directly and indirectly through mechanisms that act as serotoninergic and muscarinic receptors. Thymol, the active component of Nigella Sativa, is known to have a role and can reduce blood pressure through work on calcium ion channels. Peixoto et al. reported that thymol produced a relaxing effect in aortic mice [18].

Changes of mean diastole in preeclampsia by administration of black cumin extract (Nigella sativa)

Based on research conducted by Huseini et al., 2013 it was found that consumption of 5 ml of Nigella sativa every day can reduce diastolic by decreasing 12.46%. This was also done by Indrawan et al. in 2016, they found that a significant difference was found in endothelin 1 (ET-1) levels in rats with preeclampsia. Reduction of ET-1 by black cumin (Nigella sativa) can reduce levels of ET-1 by inhibiting the formation of peroxynitrite, which can reduce endothelial dysfunction [9].

According to the study of Sahebkar et al., 2016 daily consumption of Nigella Sativa dose of 5 ml can reduce blood pressure both systole and diastole in normal patients without any accompanying effects on the liver and kidneys. Obtained a decrease in systolic blood pressure (8.17%) and a decrease in systolic blood pressure (12.46%). Another mechanism that occurs as a blood pressure reduction effect is the diuresis effect of Nigella Sativa, from a dose of 0.6 ml/kg for 15 d can cause increase in diuresis about 16% spontaneously in hypertensive rats. The diuresis effect of Nigella Sativa compared to 5 mg/kg of dithymoquinone, and thymol have many uses. Black cumin is also known as a cure for all kinds of diseases. With the results of this study, black cumin can be recommended to be given to pregnant women both at risk and not, to prevent the occurrence of preeclampsia, given the side effects that do not exist. Black cumin is proven to reduce systolic and diastolic blood pressure, Mean Arterial Pressure and proteinuria.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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