

# EFFECTIVENESS OF RADISH (*Raphanus sativus*) EXTRACT IN REDUCING TNF- $\alpha$ AND NITRIC OXIDE LEVELS IN TYPE II DM RAT MODELS WITH TRAUMATIC BRAIN INJURY

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## ABSTRACT

**Introduction:** The devastating effects of traumatic brain injury (TBI) are fatal, and there is no effective treatment for primary brain injury, especially in patients with diabetes mellitus (DM). Nitric oxide (NO) is a compound that causes systemic vasodilation; a decrease in NO reduces cerebral blood flow after TBI. There is an increase in TNF- $\alpha$  levels demonstrated by mononuclear cells surrounding the traumatic lesion in the rat brain. *Raphanus sativus* (radish) is a root vegetable belonging to the Brassicaceae family, which has anti-diabetic effects by lowering blood glucose levels, reducing lipid peroxidation, and improving brain function, thereby protecting against neurotoxic effects associated with oxidative stress in experimental mouse models. **Objective:** To evaluate the efficacy of radish extract (*Raphanus sativus*) in reducing TNF- $\alpha$  and nitric oxide levels in a rat model of type II diabetes mellitus with traumatic brain injury. **Method:** This study was an in vivo laboratory experimental study with a post-test only control group design. The study population consisted of 25 Wistar rats, which were then induced with diabetes and subjected to a modified Feeney Model closed head injury. After complete data collection, KGD and ELISA assessments were performed, followed by data analysis. **Results:** There were significant differences ( $p < 0.05$ ) in serum NO and serum TNF- $\alpha$  levels between the normal group, the 100 mg/kg radish extract group, the 300 mg/kg radish extract group, and the 500 mg/kg radish extract group compared to the negative control group. This indicates that radish extract, starting at a dose of 100 mg/kg, can reduce serum NO and serum TNF- $\alpha$  levels.

**Conclusion:** Radish extract (*Raphanus sativus*) is effective in reducing TNF- $\alpha$  and nitric oxide levels in a Wistar rat model of type II DM with traumatic brain injury.

**Keywords:** *Diabetes Mellitus, Nitric Oxide, Raphanus sativus, TNF- $\alpha$ , Traumatic Brain Injury, Wistar Rats*

## INTRODUCTION

Radish is a type of vegetable plant in the form of tubers from the Cruciferaeaceae or Brassicaceae family.<sup>1</sup> This plant grows in temperate tropical regions. The composition of radish has high nutritional value and can also be used as an alternative medicine for various diseases including diabetes, hyperlipidemia, coronary heart disease and cancer.<sup>2</sup>

Radish has been identified as having antidiabetic effects. Radish extract promotes the synthesis of adiponectin, which is a core and regulatory protein that regulates the metabolism of lipids and glucose secreted by adipose tissue. In addition, the content of polyphenols such as catechin in radish can increase insulin secretion. Radish can also increase the synthesis of

superoxide dismutase (SOD) and endogenous glutathione and catalase enzymes that bind free radicals and prevent the peroxidation of lipids in diabetic conditions. Another study showed that radish administration can improve abnormal lipid and glucose homeostasis in HFD-induced obese rats. These improvements were associated with decreased serum lipids, hepatic TG and TC accumulation, and hepatic lipogenic gene expression.<sup>3</sup>

Radish extract is also noted as a hepatoprotective agent. Bioactive compounds, such as indole-3-carbinol, 3-[ethoxy-(methylthio)methyl]-2-pyrrolidinethione and 3-(E)-(methylthio)-methylen-2-pyrrolidineethione, which are present in flax roots and shoots reduce the severity of fatty liver disease in mouse models. In addition, black radish extract alleviated the negative effects of liver damage induced by carbon tetrachloride (CCl<sub>4</sub>) in rats. Administration of radish extract resulted in the suppression of lipid accumulation caused by oxidative stress.<sup>4</sup> Radish extract can also be used as an antioxidant. A study showed that radish extract decreased the production of NO and pro-inflammatory cytokines by LPS-activated microglia, and this can microglial neurotoxicity on nerve cells. These results suggest that the extract, through inhibition of microglial over-activation, may protect neurons from destruction by microglia-secreted pro-inflammatory and neurotoxic factors and act as an effective supplement for the prevention or treatment of neurodegeneration.<sup>5</sup>

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action or both. Broadly, diabetes mellitus is grouped into 2 main categories, namely type 1 diabetes mellitus (DM type 1) and type 2 diabetes mellitus (DM type 2).<sup>6</sup> WHO reports that in the last 3 decades, the prevalence of type 2 DM has increased dramatically worldwide. At least 422 million people in the world suffer from diabetes, especially in low- and middle-income countries.<sup>7</sup> Broadly speaking, the pathogenesis of hyperglycemia is caused by eleven causes, called 'the egregious eleven', namely: 1) Pancreatic beta cell failure; 2) Pancreatic alpha cell dysfunction; 3) Fat cells; 4) Muscle; 5) Liver; 6) Brain; 7) Colon/Microbiota; 8) Small intestine; 9) Kidney; 10) Stomach; 11) Immune System.<sup>8</sup>

Insulin resistance and abnormal secretion of insulin are the main culprits in the development of type 2 DM. Type 2 DM has a strong genetic component. Individuals with parents who have type 2 DM have a 40% risk of developing the disease. A report based on the Framingham Offspring Study found that if one parent has diabetes, the relative risk in the offspring is 3.6. If both parents have diabetes, the relative risk increases to 6.0. From this study, it can be indicated that the risk of diabetes for girls and boys is the same, regardless of whether the father or mother has diabetes.<sup>9,10</sup>

Head injuries can result in traumatic brain injuries (TBI) of different severity. TBI can generally be classified as closed head injury (CHI) or penetrating head injury (PHI).<sup>11</sup> Based on morphology, TBI can be classified into: 1) epidural hematoma; 2) subdural hematoma; 3) subarachnoid hemorrhagic; 4) intracranial hemorrhagic.<sup>12</sup> Meanwhile, based on the degree of severity, TBI can be classified based on the Glasgow Coma Scale (GCS), and is divided into 3 groups, namely: 1) Mild (14-15); 2) Moderate (9-13); 3) Severe (3-8).<sup>13</sup> In the United States in 2013, more than 1 in 50 adults aged 75 years and older experienced TBI. Men in developing countries have a much higher risk of TBI compared to developed countries.<sup>14</sup>

Neural tissue damage associated with TBI falls into two categories: (i) primary injury, which is directly caused by mechanical forces during the initial injury; and (ii) secondary injury, which refers to further tissue and cellular damage after the primary injury.<sup>15</sup> Following primary brain injury, a cascade of cellular and biochemical events occur that include the release of glutamate into the presynaptic space resulting in the activation of N-methyl-D-aspartate,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, and other receptors. These ionic shifts can activate cytoplasmic and nucleus enzymes, resulting in mitochondrial damage, and cell death and necrosis.<sup>16</sup> The biochemical, cellular and physiological events that occur during primary injury often develop into delayed and prolonged secondary damage that can last hours to years. Mechanistically, a number of factors contribute to secondary

injury, which include excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axon degeneration, and apoptotic cell death.<sup>15,16</sup>

There is currently no effective treatment to reverse the effects of primary brain injury sustained, and treatment aims to minimize secondary brain injury that can occur due to the effects of ischemia, hypoxia and increased intracranial pressure. Such effects can occur rapidly within hours, days or after further head injury.<sup>17</sup>

After TBI, glucose metabolism at the brain level is impaired, and it has been observed that insulin has a significant impact on metabolism, especially in the motor cortex. Tumor necrosis factor (TNF) reduces insulin-induced phosphorylation of the receptor, insulin receptor substrate proteins, protein kinase B/AKT, glycine kinase-3 synthase, GLUT4 activation, and inadequate activation of the glucose synthase system, despite higher energy demand after TBI. This leads to relative insulin deficiency, changes in energy metabolism, and ultimately cell death. The insulin receptor pathway contributes to the repair of small, myelinated fibers by increasing mitochondrial membrane potential and ATP production, while at the same time reducing NADPH and hexokinase activity.<sup>18</sup>

The cause of hyperglycemia after TBI is multifactorial. The acute sympathetic response leads to increased serum levels of catecholamines, which cause a rise in blood glucose levels by increasing glycogenolysis in skeletal muscles and liver tissue, increasing gluconeogenesis, and inhibiting insulin secretion. Elevated levels of cortisol and cytokines such as interleukin-6 may also contribute to hyperglycemia in these patients. Traumatic brain injury also leads to generalized metabolic dysfunction in the brain, where glucose requirements increase to meet the needs associated with trauma recovery resulting in a condition of hyperglycolysis, and insulin resistance similar to patients with type 2 diabetes mellitus. This energy crisis is associated with increased susceptibility to the harmful effects of brain injury.<sup>19,20,21</sup>

Hyperglycemia between 135 and 200 mg/dl during intake has been associated with infections, increased hospital stay, and increased mortality rates. Moreover, hyperglycemia within the first 24 hours has been identified as an independent risk factor that increases mortality rates and has suggested early therapeutic intervention regardless of injury severity (as measured by the Glasgow Coma Scale). Persistent hyperglycemia aggravates patients with TBI, increasing the duration of stay in intensive care and being a significant risk factor for mortality. Insulin has been used in intensive therapy for hyperglycemia management and has been associated with severe hypoglycemia conditions. To counter this effect, it has been suggested to accompany high doses of insulin with a glucose supply, which in turn avoids insulin deficiency. It is important to maintain proper blood glucose levels to optimize outcomes and minimize complications.<sup>21,22,23</sup>

## METHODS

This study is an in vivo laboratory experiment with a post test only control group design with a complete randomized design method. Sampling was carried out with the principle of non-probability sampling by consecutive sampling and there was a comparison control. The samples used were rats that had gone through the acclimatization and adaptation process. This research was conducted at the Faculty of Medicine and Integrated Lab of Universitas Sumatera Utara, and will be carried out after obtaining approval and the Health Research Ethics Committee of Universitas Sumatera Utara.

In this study, 25 Wistar rats, 5 weeks old and weighing between 180-200 g, were obtained from the Pharmacology Laboratory, Faculty of Medicine, Universitas Sumatera Utara. The experimental phase began when the body weight of the rats reached between 250-300 g.

The samples were divided into five groups with 5 rats in each group, based on the treatments of DM induction, closed head injury model administration, and radish extract administration. Diabetes was induced by a single intraperitoneal injection of Streptozotocin (STZ; 65 mg/kg body weight, Sigma-Aldrich, Germany) solution in 0.1 mol/L sodium citrate buffer (pH = 4.5). To confirm diabetes, on the third day after STZ injection, blood samples were collected

via the rat tail vein technique using heparinized glass capillary tubes, and plasma glucose levels were measured with the GOD-POD enzyme diagnostic kit method (Accurex®, India). Animals were considered diabetic if blood glucose values were above 300 mg/dL. A closed head injury trauma model was performed using a modified Feeney Model by dropping a 40 mg metal weight from a height of 1.5 m for the traumatic brain injury model. Each treatment group on day 8 was killed and the brain was taken and then blood serum was taken to examine the levels of TNF Alpha and NO by Enzyme Linked Immuno Assay (ELISA) method with units of pg/ml.

The independent variable in this study is the variation of the amount of radish extract given, while the dependent variable is the result of blood (sugar level, TNF alpha, nitric oxidase) and brain (TNF alpha and nitric oxidase) examination. Measurement of blood sugar levels was carried out every day after giving radish extract to find out how changes in blood sugar levels during one week of giving radish extract. Measurement of NO and TNF alpha levels was carried out using two methods, namely ELISA derived from blood.

The research data that has been obtained, processed, edited and tabulated is then tested for normality using the Saphiro-Wilk test. If the data is normally distributed, then proceed with one-way ANOVA testing with a significance level of 95%. If the ANOVA test shows  $p < 0.05$ , then proceed with the post hoc test to determine the differences between each group. If the data is not normal, then proceed with nonparametric testing, namely Kruskal Wallis followed by multiple pairwise comparison tests to determine the differences between each group. Data analysis processing was carried out using SPSS 26.0 for Windows.

## RESULTS

### Results of blood sugar level data analysis

This study found that the normal group obtained an average glucose of  $90.6 \pm 14.12$  mg/dL, negative group with an average of  $274.8 \pm 33.66$  mg/dL, positive group with an average of  $120.8 \pm 10.26$  mg/dL, 100 mg/kg extract group with an average of  $230.6 \pm 10.5$  mg/dL, 300 mg/kg group with an average of  $192 \pm 33.35$  mg/dL, and 500 mg/kg group with an average of  $139 \pm 11.89$  mg/dL. In addition, it is also known that overall there are significant differences ( $p < 0.001$ ) between all treatment groups.

**Table 1.** Glucose levels

| Groups    | Glucose levels (mg/dL) | P-value |
|-----------|------------------------|---------|
| Normal    | $90.6 \pm 14.12$       | P<0.001 |
| Negative  | $274.8 \pm 33.66$      |         |
| Positive  | $120.8 \pm 10.26$      |         |
| 100 mg/kg | $230.6 \pm 10.5$       |         |
| 300 mg/kg | $192 \pm 33.35$        |         |
| 500 mg/kg | $139 \pm 11.89$        |         |

The analysis was then continued with the Posthoc Tukey test to determine the difference in blood sugar levels between each treatment group. It was found that there was a significant difference ( $p < 0.05$ ) between the normal, positive, radish extract 300 mg/kg, and 500 mg/kg groups with the negative group. This indicates that radish extract starting with a dose of 300 mg/kg showed antidiabetic effects. In addition, the 500 mg/kg dose of horseradish extract did not have a significant difference with the normal group ( $p = 0.133$ ) and the positive group ( $p = 0.909$ ), indicating that the 500 mg/kg dose of horseradish extract has an antidiabetic ability

that is not statistically different from the positive group receiving a 20 mg/kg dose of metformin.

**Table 2.** Glucose Levels Posthoc Test

| Groups    | Normal | Negative | Positive | 100 mg/kg | 300 mg/kg | 500 mg/kg |
|-----------|--------|----------|----------|-----------|-----------|-----------|
| Normal    |        | P<0.001* | 0.556    | P<0.001*  | P<0.001*  | 0.133     |
| Negative  |        |          | P<0.001* | 0.195     | 0.003*    | P<0.001*  |
| Positive  |        |          |          | P<0.001*  | 0.007*    | 0.909     |
| 100 mg/kg |        |          |          |           | 0.309     | P<0.001*  |
| 300 mg/kg |        |          |          |           |           | 0.085     |
| 500 mg/kg |        |          |          |           |           |           |

**Results of Serum Nitric Oxide Data Analysis**

The study found that the normal group obtained a mean serum NO of  $13.2 \pm 1.3$  umol/L, the negative group with a mean of  $21.8 \pm 1.3$  umol/L, the positive group with a mean of  $19.6 + 1.82$  umol/L, the 100 mg/kg extract group with a mean of  $17.4 \pm 1.14$  umol/L, the 300 mg/kg group with a mean of  $15 \pm 0.71$  umol/L, and the 500 mg/kg group with a mean of  $13.8 \pm 0.84$  umol/L. In addition, it is also known that overall there are significant differences ( $p<0.001$ ) between all treatment groups.

**Table 3.** NO Serum levels

| Groups    | NO serum (umol/L) | P-value |
|-----------|-------------------|---------|
| Normal    | $13.2 \pm 1.3$    |         |
| Negative  | $21.8 \pm 1.3$    |         |
| Positive  | $19.6 \pm 1.82$   | P<0.001 |
| 100 mg/kg | $17.4 \pm 1.14$   |         |
| 300 mg/kg | $15 \pm 0.71$     |         |
| 500 mg/kg | $13.8 \pm 0.84$   |         |

The analysis was then continued with the Posthoc Tukey test to determine the difference in blood sugar levels between each treatment group. It was found that there was a significant difference ( $p<0.05$ ) between the normal group, radish extract 100 mg/kg, radish extract 300 mg/kg, and 500 mg/kg with the negative group. This indicates that radish extract starting with a dose of 100 mg/kg can reduce serum NO. Then, if further considered, radish extract doses of 300 mg/kg ( $p=0.104$ ) and 500 mg/kg ( $p=0.903$ ) did not have a significant difference with the normal group ( $p=0.133$ ), this indicates that radish extract doses of 300 mg/kg and 500 mg/kg can reduce serum NO to approach normal conditions without treatment.

**Table 4.** Posthoc Test of NO Serum Level

| Groups    | Normal | Negative | Positive | 100 mg/kg | 300 mg/kg | 500 mg/kg |
|-----------|--------|----------|----------|-----------|-----------|-----------|
| Normal    |        | P<0.001* | P<0.001* | P<0.001*  | 0.104     | 0.903     |
| Negative  |        |          | 0.090    | P<0.001*  | P<0.001*  | P<0.001*  |
| Positive  |        |          |          | 0.090     | 0.007*    | 0.909     |
| 100 mg/kg |        |          |          |           | 0.017*    | P<0.001*  |
| 300 mg/kg |        |          |          |           |           | 0.430     |
| 500 mg/kg |        |          |          |           |           |           |

### Results of Serum TNF- $\alpha$ Data Analysis

In this study, it was found that in the normal group, the mean serum TNF- $\alpha$  was  $104.6 \pm 6.88$  pg/mL, the negative group with a mean of  $235.4 \pm 16.64$  pg/mL, the positive group with a mean of  $135.2 \pm 13.65$  pg/mL, the 100 mg/kg extract group with a mean of  $174.8 \pm 6.09$  pg/mL, the 300 mg/kg group with a mean of  $156.4 \pm 20.78$  pg/mL, and the 500 mg/kg group with a mean of  $112 \pm 7.71$  pg/mL. In addition, it is also known that overall there are significant differences ( $p < 0.001$ ) between all treatment groups.

**Table 5.** TNF- $\alpha$  levels

| Groups    | Serum TNF- $\alpha$ (pg/mL) | P-value |
|-----------|-----------------------------|---------|
| Normal    | $104.6 \pm 6.88$            | P<0.001 |
| Negative  | $235.4 \pm 16.64$           |         |
| Positive  | $135.2 \pm 13.65$           |         |
| 100 mg/kg | $174.8 \pm 6.09$            |         |
| 300 mg/kg | $156.4 \pm 20.78$           |         |
| 500 mg/kg | $112 \pm 7.71$              |         |

The analysis was then continued with the Posthoc Tukey test to determine the difference in blood sugar levels between each treatment group. It was found that there was a significant difference ( $p < 0.05$ ) between the normal group, positive horseradish extract 100 mg/kg, horseradish extract 300 mg/kg, and 500 mg/kg with the negative group. This shows that radish extract starting with a dose of 100 mg/kg can reduce serum TNF- $\alpha$ . In addition, horseradish extract doses of 300 mg/kg ( $p = 0.150$ ) and 500 mg/kg ( $p = 0.895$ ) did not have significant differences with the positive group, indicating that horseradish extract doses of 300 mg/kg and 500 mg/kg have anti-inflammatory abilities that are not statistically different from the positive group receiving metformin dose of 20 mg/kg. Then, it is also known that 500 mg/kg horseradish extract is not significantly different ( $p = 0.895$ ) with the normal group, this indicates that the anti-inflammatory ability of horseradish extract is better than metformin.

**Table 6.** Posthoc test of TNF- $\alpha$  levels

| Groups | Normal | Negative | Positive | 100 mg/kg | 300 mg/kg | 500 mg/kg |
|--------|--------|----------|----------|-----------|-----------|-----------|
|--------|--------|----------|----------|-----------|-----------|-----------|

|          |  |          |          |          |          |          |
|----------|--|----------|----------|----------|----------|----------|
| Normal   |  | P<0.001* | 0.013*   | P<0.001* | P<0.001* | 0.895    |
| Negative |  |          | P<0.001* | P<0.001* | P<0.001* | P<0.001* |
| Positive |  |          |          | 0.001    | 0.150    | 0.094    |
| 100      |  |          |          |          | 0.210    | P<0.001* |
| mg/kg    |  |          |          |          |          |          |
| 300      |  |          |          |          |          |          |
| mg/kg    |  |          |          |          |          | P<0.001* |
| 500      |  |          |          |          |          |          |
| mg/kg    |  |          |          |          |          |          |

## DISCUSSION

### Effect of Radish Extract on Blood Sugar Levels

Radish has been known to have diabetic effects through various in-vitro and in-vivo studies. Radish is known to contain anthocyanins, a potent flavonoid antioxidant that can improve conditions in diabetic patients. Radish can lower blood sugar levels through several methods. Radish plays a role in increasing the production of adiponectin, which regulates glucose and fatty acids. Radish is also known to lower plasma insulin in normal rats and diabetic model rats with streptozocin by increasing insulin sensitivity or mimicking the effects of insulin without increasing insulin production.<sup>24,25,26,27</sup>

Elnour et al in 2022 examined the comparison of blood glucose changes in rats given 250 mg/kg sugar. After giving 250 mg/kg dose of radish extract with 10 mg/kg dose of glibenclamide, it was found that radish extract can reduce glucose ( $94.60 \pm 4.523$  mg/dL) clinically better than glibenclamide ( $112.6 \pm 2.42$  mg/dL) within 4 hours.<sup>26</sup> Another study by Narvaez et al 2024 proved that radish can reduce body weight, improve glucose regulation, and protect the pancreas and liver in rats given a high-sucrose diet.<sup>28</sup>

### Effect of Radish Extract on Serum Nitric Oxide

Radish has the ability of defense mechanisms using antioxidants and reducing oxidative stress when there is an imbalance of oxidative stress and antioxidants in the cellular system. The increase in nitric oxide right after TBI is the brain's mechanism to lower intracranial pressure by reducing neuroinflammation.<sup>29,30,31</sup>

Papadimos et al (2009) reported that the use of inhaled NO in patients with TBI and ARDS was proven to reduce the inflammatory response in TBI patients with increased ICP, thereby improving patient outcomes.<sup>32</sup> In a study conducted by Lenz et al (2020), it is known that increased NO can prevent secondary brain damage.<sup>33</sup> In a study conducted by Subedi et al (2021), it is known that NO plays a role in neuroinflammation because it increases the production of free radicals which can affect cellular integrity due to mitochondrial damage.<sup>34</sup> In a review published by Tripodi et al (2025), it is known that NO has two roles as neuroprotection and neurodegeneration.<sup>35</sup>

Excessive increase in NO can increase neuroinflammation and oxidative damage, however, when NO production increases along with nitrate consumption, it can increase bioavailability through the nitrate-nitrite-NO pathway and mitigate inflammation and oxidative damage so

nitrate consumption is known to modulate the level.<sup>35</sup>

#### **Effect of Radish Extract on Serum TNF- $\alpha$**

Radish extract shows important potential in lowering TNF- $\alpha$  levels, which has implications for various inflammatory conditions and neurodegenerative processes. Research shows that radish extract significantly reduces TNF- $\alpha$  gene expression in human keratinocyte cell lines. Radish extract can decrease mRNA expression and secretion of inflammatory cytokines, including TNF- $\alpha$ , in microglia activated by lipopolysaccharide (LPS).<sup>36</sup> Radish extract can inhibit excessive activation of microglia. By inhibiting this activation, horseradish extract may protect neuronal cells from neurotoxicity caused by microglia activation.<sup>37</sup>

Radish extract showed promising results in reducing TNF- $\alpha$  levels through various mechanisms, including direct decrease in gene expression and inhibition of microglia activation, indicating its potential use in treating inflammatory and neurodegenerative conditions.<sup>36,37</sup>

#### **CONCLUSION**

Radish extract (*Raphanus sativus*) is effective in reducing glucose levels, TNF- $\alpha$  and nitric oxide levels in a type II DM rat model with traumatic brain injury. Radish extract starting with a dose of 300 mg/kg showed antidiabetic effects. Radish extract at a dose of 500 mg/kg has antidiabetic ability that is not statistically different ( $p > 0.05$ ) with the positive group receiving metformin at a dose of 20 mg/kg, even approaching glucose levels in the normal group without treatment. Radish extract starting with a dose of 100 mg/kg can reduce serum NO in a type II DM rat model with traumatic brain injury. Then, horseradish extract doses of 300 mg/kg and 500 mg/kg can reduce serum NO to approach normal conditions without treatment. Radish extract starting with a dose of 100 mg/kg can reduce serum TNF- $\alpha$ . Radish extract doses of 300 mg/kg and 500 mg/kg have anti-inflammatory abilities that are not statistically different ( $p > 0.05$ ) with the positive group receiving metformin dose of 20 mg/kg. The 500 mg/kg dose of radish extract ( $112 \pm 7.71$  pg/mL) even had better anti-inflammatory ability than the 20 mg/kg dose of metformin ( $135.2 + 13.65$  pg/mL).

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