



## The Nephroprotector Effect of Sukari Date (*Phoenix dactylifera*) Extract on Meloxicam Induced in Rats

Amelia Ramadhani Anshar\*, Muhammad Ardiansyah Nurdin, Rizky Widiyanti, Mutmainnah Subakir, Andi Tenri Khofifah, Dwiyuca Fauziah

Study Program of Veterinary Medicine, Faculty of Medicine, Hasanuddin University, Jl. Perintis Kemerdekaan Km. 10, Makassar, 90245, Indonesia

\*Corresponding author: [ameliaanshar@med.unhas.ac.id](mailto:ameliaanshar@med.unhas.ac.id)

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### Abstract

*Drug poisoning in pets can cause serious kidney damage due to high levels of free radicals in body against the toxicity. Prevention of kidney damage can be solved by using of some exogenous antioxidants. Sukari dates (*Phoenix dactylifera*) are reported able to reduce off free radicals with antioxidant active ingredients in such as flavonoids, phenolics, vitamins C, A, E, and B-carotene. This study aims to determine the effect of Sukari date extract as a nephroprotector agent in reducing blood urea nitrogen (BUN) levels after meloxicam induced. This experimental study with a completely randomized design used 24 male white rats of wistar strain which were divided into 4 treatment groups. Group 1 (K1) is a negative control group given 1% NaCMC, group 2 (K2) is a positive control group given 2 ml at a dose of 30 mg/kgBW meloxicam, treatment group 1 (P1) and treatment group 2 (P2) were each given 2 ml of Sukari date extract at a dose of 500 mg/kgBW and 1000 mg/kgBW for 11 days. Meloxicam induction dose of 30 mg/kgBW was given on the 12th day, BUN levels were measured on the 13th day and 15th day with a spectrophotometer. BUN concentration of mean in control groups K1 was  $19.54 \pm 0.828$ , K2 group was  $41.55 \pm 0.534$ , the treatment group P1 was  $24.86 \pm 0.715$  and P2 was  $20.48 \pm 0.383$ . These results indicate that the administration of Sukari date extract was able to maintain BUN levels at normal levels even though they had been exposed to toxic doses of meloxicam.*

**Key words:** Antioxidants, Blood Urea Nitrogen (BUN), Sukari dates, meloxicam

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### Introduction

Damage organ in body caused by the body being unable to neutralize free radical molecules that are formed. One of the negative effects of the accumulation of free radicals is kidney damage. Kidney damage can be caused by chemical contamination, drugs toxicity, fungi, bacteria or viruses. One example of drug toxicity that can contribute to kidney damage is meloxicam which is efficacious as an analgesic, antipyretic and non-steroidal anti-inflammatory (Pawlukianiec *et al.*, 2020; Coldits *et al.*, 2019; Geof at al, 2008). Meloxicam is a new generation of Non-Steroid Anti-Inflammatory Drugs (NSAIDs) which are classified as extra-label drugs, where according to Farad (Food Animal Residue Avoidance Databank) there have been many cases of kidney failure, impaired liver function, and death in cats associated with repeated use of Meloxicam. (Patty *et al.*, 2016; Geof et al., 2008). Therefore, if the administration is

given more than the normal recommendation, there will be an acute or chronic overdose of meloxicam which can cause damage to the kidneys, liver and also gastrointestinal ulcers (Colditz *et al.*, 2019; Polloct *et al.*, 2012).

Indonesian people usually consumed some plants as ingredients for herbal medicines, one of which is dates (*Phoenix dactylifera*) as antioxidants with active ingredients of phenolic compounds and flavonoids used to treat acute kidney failure (Hussain *et al.*, 2020). Dates have an important role in neutralizing free radicals (Rahmani, *et al.*, 2014). Free radicals and oxidative damage can be prevented by administering exogenous antioxidant compounds, by giving hydrogen atom groups to unpaired free electrons so that they can become stable (Saryono and Dwi, 2015).

Dates are a good source of antioxidants because they contain active compounds such as alkaloids, flavonoids, steroids, tannins, estertepene, carbohydrates, vitamins, phenolic acids, B-carotene, sugar, protein, fat, fiber, potassium, calcium, iron, chlorine, copper, magnesium, sulfur, phosphorus, and several enzymes (Ghori *et al.*, 2018). Research results of Rahmani *et al.* 2014 explained that rats with nephrotoxicity were then given date extract of the Ajwa variety showed a significant decrease in serum creatinine and urea levels and could repair proximal renal tubular damage. The content in dates that are used to treat acute kidney failure are flavonoids and phenolics in polyphenol compounds (Wulan, 2018). From this study, dates are known to contain flavonoids and phenolics which are efficacious as kidney protection from toxic compounds or known as nephroprotective. Therefore, based on the background and considerations above, this study wanted to examine the nephroprotector effect of the date palm extract (*Phoenix dactylifera*) on BUN and creatinine levels in meloxicam-induced rats.

## Materials and Methods

### *Materials*

This study used is an experimental method with a completely randomized design consisting of 2 control groups (K1 and K2) and 2 treatment groups (P1 and P2). The variables in this study were Sukari Dates Extract (*Phoenix dactylifera*) in independent variables with BUN as dependent variables. Controlled variables in this study were male rats including strain, age, body weight, treatment and maintenance environment.

The experimental animals used in this study were adult male rats of Wistar strain aged 3 months with a body weight around 200 grams then 24 rats were randomly divided into 6 rats for each group. Rats were sourced from the *Commercial Breeder Rat and Mice*. Animals were first acclimatized for 10 days to adjust new environment.

### *Method*

Sukari dates was separated from the seeds, then it was dried for 2 weeks in a drying cabinet at 60°C temperature. The dried date then cut into small pieces and mashed using a blender machine. About 2 kg of dried date flesh was put into a glass vessel and soaked in 5 liters of 96% ethanol (all parts submerged) for 5 days, stirring occasionally. After soaking for 5 days, the marinade was filtered using a Buchner vacuum lined with filter paper. The macerate is stored for further evaporation using a rotary evaporator at a temperature of 600C and placed on a water bath until a thick extract is formed (Roznizar *et al.*, 2015).

Meloxicam in the form of a solution made from meloxicam tablets was weighed according to the toxic dose (single) for each rat of 30 mg/kgBW (Anshar *et al.* 2017), dissolved in 1% Na

CMC solution as a meloxicam carrier. In 1 ml of the meloxicam solution, it takes 0.01 g of Na CMC powder mixed with 30 mg x body weight (BW) of rats (in kg), and dissolved in aquadest until 1 ml is obtained.

Doses of Sukari date extract was determined through *trial error* observations on experimental animals, the dose levels obtained for each treatment group where the first dose was given 500 mg/KgBW of Sukari date fruit extract and the second dose was given 1000 mg/KgBW Sukari date fruit extract. Sukkari date fruit extract was dissolved with 1% NaCMC. The positive control group and each treatment group were induced with meloxicam suspension orally on day 12.

Group 1 (K1) is a negative control group of experimental animals treated with 1% 2 ml NaCMC. Group 2 (K2) is a positive control group where experimental animals were given NaCMC 1% 2 ml for 11 days and on the 12th day meloxicam 30 mg/kgBW was induced. Treatment group 1 (P1) and treatment group 2 (P2) were each treated with 2 ml of dates extract at a dose of 500 mg/kgBW and 1000 mg/kgBW for 11 days and on the 12th day meloxicam was induced at a dose of 30 mg/kgBW. BUN and Creatinine levels were measured on day 13 and day 15.

Measurement methods of BUN as follows, blood samples taken 2 times (after the administration of meloxicam and 2 days after with each volume of 1ml - 2ml. Each blood sample was placed on a 5 ml plain sample bottle that had been labeled and allowed to stand for 15 minutes. The blood sample was centrifuged for 5 minutes at a rate of 5000 rpm to separate serum from blood cells. After the serum is separated from plasma, the serum is inserted in a newly labeled serum cup. Each cup is inserted into The Advia Chemistry XPT system Siemens Healthcare Tarritown - NY, which is a tool used to measure BUN levels.

Observations and records were performed on BUN in male white blood observed at the time of meloxicam administration on day 11th and two days after it on day 13th. The data obtained were treated with Anova One Way and if significantly different were followed by T-Test to see the difference of BUN levels among the groups from control groups and treatment groups to Sukari Date effect

## Results and Discussion

Experimental animals as many as 24 male rats were acclimatized before proceeding to the treatment stage. Acclimatization was carried out for 10 days with the provision of commercial drinking Club brand and BR-1 feed *ad libitum* (Angria, 2019). The acclimatized rats were given treatment according to the predetermined group. Group 1 (K1) is a negative control group of experimental animals treated with 1% 2 ml NaCMC. Group 2 (K2) is a positive control group where experimental animals were given NaCMC 1% 2 ml for 11 days and on the 12th day meloxicam 30 mg/kgBW was induced. Treatment group 1 (P1) and treatment group 2 (P2) were each treated with 2 ml of dates extract at a dose of 500 mg/kgBW and 1000 mg/kgBW for 11 days and on the 12th day meloxicam was induced at a dose of 30 mg/kgBW. BUN levels were measured on day 13 and day 15.

Based on Table 1, it is known that the average BUN level at the initial examination (24 hours after meloxicam administration) for group K1 was 19.28 mg/dl (SEM: 0.67), group K2 had an average BUN value of 41.23 mg/dl (SEM: 0.452), while the P1 group had an average BUN value of 25.04 mg/dl (SEM: 0.61) and the P2 treatment group had a value of 22.35 mg/dl (SEM: 0.705). The increase in BUN levels after administration of meloxicam 30 mg/kgBW could be seen in the positive control group K2 which showed an increase in the number from the normal value of 41.23 mg/dl. Meanwhile, the P1 treatment group and the P2 treatment group

showed values that were close to the maximum limit of BUN levels in the blood with values of 25.04 mg/dl and 22.35 mg/dl respectively, but still within the normal range for BUN levels in rats.

Measurement of kidney damage of BUN levels showed that there were significant differences belong to concentration levels in each group. The average concentration of BUN is presented in Table 1.

Tabel 1 The mean level of BUN in control group and treatment group

| Group | BUN levels (mg/dl)       |                          |
|-------|--------------------------|--------------------------|
|       | 1st                      | 2nd                      |
| K1    | 19.28±0.67 <sup>a</sup>  | 19.54±0.828 <sup>a</sup> |
| K2    | 41.23±0.452 <sup>b</sup> | 41.55±0.534 <sup>b</sup> |
| P1    | 25.04±0.61 <sup>a</sup>  | 24.86±0.715 <sup>a</sup> |
| P2    | 22.35±0.705 <sup>c</sup> | 20.48±0.383 <sup>c</sup> |

Note : \* BUN levels (normal 13.9-28.3 mg/dl) were obtained from 6 replications. The same superscript letter in the column shows results that are not significantly different (p>0.05)

The increase in BUN levels due to the administration of a toxic dose of meloxicam in this study is in line with the results of a study conducted by Anshar *et al.*, 2018 which showed that the nephrotoxic effect of a toxic dose of meloxicam was associated with metabolic disorders in the form of disturbances in the electrolytes in the BUN so that it increased. The increase in the BUN value is a compensation from the body due to the use of toxic doses of meloxicam which causes tissue damage associated with glutathione depletion significantly and lipid peroxidation occurs, resulting in intracellular accumulation and high binding of reactive metabolites, cell damage and even death. *et al.*, 2020; Adeneye *et al.*, 2008; Schnellman, 2001), besides that meloxicam also triggers apoptosis in kidney cells (Boularea *et al.*, 2002; Ray and Jena, 2000). This study is also evidence in membrane activity and even necrosis of mitochondrial membrane in the kidney due to exposure to meloxicam toxic in an acute phase.

Based on final measurement results (2 days after meloxicam induction), it was found that the positive control group K2 still showed an increase in BUN levels with a value of 41.55 mg/dl (SEM: 0.534), while the negative control group K1 showed normal BUN levels with levels of 19.54. mg/dl (SEM: 0.828), treatment group P1 of 24.86 mg/dl (SEM: 0.715) and treatment group P2 with BUN levels of 20.48 mg/dl (SEM: 0.383). These results indicate that the ability of the Sukari date extract to maintain BUN levels in the P1 and P2 treatment groups remained in the normal range of BUN levels despite exposure to toxic doses of meloxicam.

The results of this study indicate that clinically extracts of Sukari dates have the ability as a protective agent against kidney damage. The results of testing the nephroprotector effect of the Sukari Date Extract on BUN levels in rats induced by toxic doses of meloxicam showed that the Sukari Date Extract was able to overcome the increase in BUN levels. This result is evidenced by the BUN concentration value which shows that the treatment of the positive control group with a toxic dose of meloxicam resulted in an increase in the level of BUN concentration beyond the normal limit in rats. Meanwhile, the treatment group that was given the Sukari date extract at a dose of 500 mg/kgBW and 1000 mg/kgBW showed a significant difference to the positive control group. This study showed that the extract of the Sukari dates had good protective properties against the kidneys. The P2 group treated with Sukari dates extract 1000 mg/kgBW showed the best level by 24.86±0.715 better than P1 treated group with level by 20.48±0.383. This indicates that Sukari date extract in the P2 groups is an optimal dose, which is 1000 mg/kgBW is able to prevent increase of BUN and keep the concentration at the normal

levels of BUN. P2 treated group also shows protect action of kidney damage due to toxic doses of meloxicam that will increase of BUN levels.

The administration of Sukari date extract as a nephroprotector agent which has a high antioxidant content gave significantly different results from the positive control group. This shows that the Sukari date extract contains flavonoids, saponins, alkaloids, tannins and triterpenoids which are antioxidants (Hamad *et al.*, 2015; Abdelrahman, 2012). Flavonoids can directly scavenge free radicals, can inhibit enzymes that play a role in producing superoxide anions and prevent the peroxidation process by reducing peroxidation by capturing and reacting with free radicals which then give one hydrogen atom from the hydroxy group so that free radicals can be stable. , 2015; Ismail and Radzi, 2013).

Dates are an important food for nerve cells, detoxifiers of toxins, and are useful for people who experience kidney failure, high blood pressure, hemorrhoids and fatigue (Alwahshi *et al.*, 2019; Nata, 2018). In addition, a similar study conducted by Anisa 2015 stated that seven dates will create a kind of hook, so that dirt or toxins will be released from the body in the form of feces or urine.

## Conclusion

In this study, administration of Sukari dates ( *Phoenix dactylifera* ) extract has a good effect as a nephroprotector agent where the BUN concentration in the treatment group remained in the normal range after induction of meloxicam toxic dose. The optimal dose to protect increase of BUN level induced by meloxicam was 1000 mg/kgBW.

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