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# The Antioxidant Effect of Ajwa Dates (*Phoenix dactylifera L.*) to Inhibit the Progression of Preeclampsia Threats on Pregnant Women through Malondialdehyde as Prooxidant Serum Marker

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## ABSTRACT

Hypertension in pregnancy, including preeclampsia, is still a significant problem worldwide and is one of the top three causes of maternal death in Indonesia. The pathophysiology of the disease is unclear yet, but vascular dysfunction due to oxidative stress is thought to play a role. Ajwa dates are known for their antioxidant effects due to their higher phenolic and flavonoids than other dates. The study aimed to determine the effect of consuming seven Ajwa dates each day on the progression of preeclampsia as assessed by changes in malondialdehyde (MDA) levels. Forty pregnant women with gestational age ≥20 weeks were randomly assigned into two groups: the control group (n= 10), who were encouraged to consume lots of fruits and vegetables, and the intervention group (n= 30), who consumed seven pieces of Ajwa dates every day for eight weeks. MDA measurements were carried out pre- and post-intervention. The intervention group showed a significant reduction in MDA levels following the 8-week intervention period. Consumption of seven Ajwa dates every day can reduce MDA levels significantly and, thus, has the potential to inhibit the progression of preeclampsia in pregnant women who are at risk of preeclampsia based on stress oxidative mechanism.

Keywords: Ajwa dates; Preeclampsia; Malondialdehyde

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## INTRODUCTION

Maternal mortality around the world is unacceptably high. According to the World Health Organization (WHO) reports, there are approximately 810 deaths of women every single day due to pregnancy and childbirth complications. The complications that occur in the majority of the cases are severe bleeding, infection, hypertension in pregnancy, and unsafe abortion. [(1)] Hypertension in pregnancy may include chronic hypertension, preeclampsia, and eclampsia. Of these, preeclampsia is the major problem and the leading cause of fetal and maternal mortality worldwide. [(2)]

Preeclampsia is a disorder of pregnancy characterized by a new onset of hypertension after 20 weeks of gestation. The condition can be accompanied with or without the new onset of proteinuria.[(2)] It is also associated with other signs and symptoms, including blurry vision, headache, and edema. Preeclampsia can result in consequences for maternal and fetal. The maternal consequences may include cardiovascular disease, cerebrovascular disease, liver and renal failure. The fetus exposed to preeclampsia may have an increased risk of diseases such as hypertension and other cardiovascular diseases resulting from fetal growth restriction and preterm birth. [(3)]

The diagnosis of preeclampsia is based on the new onset of hypertension and proteinuria. In the absence of proteinuria, preeclampsia is diagnosed if any of the following features are present: thrombocytopenia, impaired liver function, renal insufficiency, or pulmonary edema. [(2)] A previous study revealed that the combination of body mass index (BMI), mean arterial pressure (MAP), and roll-over test (ROT) can be used as predictive factors for the development of preeclampsia in pregnant women.[(4)]

From early pregnancy, the placenta assumes a state of oxidative stress necessary for embryonic and fetal growth. Oxidative stress arises from increased placental mitochondrial activity and reactive oxygen species (ROS) production. However, excessive ROS production can damage the cell structures, including DNA, proteins, and lipids. Free ROS degrades polyunsaturated lipids to form malondialdehyde (MDA), which is used as a biomarker for oxidative stress levels.[(5)] In preeclampsia, the increase in oxidative stress is the result of repeated placental ischemia. This condition is thought to result from an inadequate invasion of fetal cytotrophoblasts, which causes a lack of vascular remodeling in the maternal spiral arteries.[(3)] Several studies have found that there are statistically significant differences in MDA levels between preeclampsia women and normotensive pregnant women.[(5–7)] Moreover, the study also shows that levels of MDA in preeclampsia women did not vary across gestation.[(5)]

Date fruits, *Phoenix dactylifera L.* are a rich source of sugars, fibers, vitamins, and minerals. It also possesses antioxidant and antimutagenic properties. Biological and nutritional analyses of 12 kinds of dates from Saudi Arabia were conducted to determine the nutritional compositions of each kind of date. The study revealed that Ajwa dates have the highest level of phenolic and flavonoids. However, the potential of Ajwa dates was not fully elucidated in preeclampsia women; thus in the present study,

we aimed to determine the effect of consuming seven pieces of Ajwa dates each day on the progression of preeclampsia as assessed by changes in MDA levels.[8]

## METHODS

This randomized control study was conducted from January 28th to March 30th, 2019. The population of the study was all pregnant women with gestational age ≥ 20 weeks who made antenatal care (ANC) visits at Sitti Khadijah 1 Muhammadiyah Hospital, Makassar, South Sulawesi, Indonesia. The research protocols were approved by the Ethical Committee of Medical Faculty, Hasanuddin University (64/UN4.6.4.5.31/PP36/2019).

The screening was performed to include the participants in this study. The inclusion criteria of this study were: (1) pregnant women having one of the preeclampsia risk factors, including obesity, primipara, history of hypertension, preeclampsia history in a previous pregnancy, and family history of preeclampsia; (2) pregnant women having predicted preeclampsia in one or both biophysical predictor assessment (MAP and ROT); (3) gestational age at ≥20 weeks; and (4) agreed to be included as study participants. The exclusion criteria included (1) having fasting blood glucose and 2-hour postprandial blood glucose beyond normal range according to WHO standards, (2) having a previous history of chronic infection diseases (i.e., tuberculosis, malaria, and thalassemia), and (3) having degenerative diseases (i.e., cardiovascular diseases, cancer chronic renal failure, and diabetes mellitus). Written informed consent was obtained from all participants.

The participants were randomly assigned to the control group, and the intervention group, receiving seven pieces of Ajwa dates daily. Determining the number of 7 pieces Ajwa dates is based on the hadith of the Prophet *"Whoever consumes seven Ajwa dates in the morning, on that day he will not be affected by poison or magic" (Sahih Al-Bukhari and Sahih Muslim).* Giving seven Ajwa dates was carried out in a study by Al Kuran *et al* (2011) who gave seven dates to pregnant women in the last trimester to see the effect on the birthing process. Likewise, Jadidi *et al*. (2015), Al Dossari *et al*. (2017), and Razali *et al*. (2017) provided the same amount in their research to determine the effect of dates on childbirth in pregnant women. In the beginning, the participants from both groups were given a counseling session that provided information on the risks of preeclampsia and the ways to manage the risk to prevent preeclampsia. However, participants in the intervention group were also provided information on the benefits of daily consumption of seven pieces of Ajwa dates every single morning for general health and pregnancy. On the other hand, participants in the control group were encouraged to consume nutritious food, avoid fast food, and increase the consumption of fruits (except dates) and vegetables. To reinforce the given information, a leaflet consisting of information on preeclampsia and Ajwa dates was provided to the intervention group. The participants in the intervention group were also given diary sheets to record their daily intake of Ajwa dates for eight weeks. Included participants can be dropped out if any of these happens: (1) Participants from both groups consuming calcium, vitamin D, or salicylic acid preparat, (2) Participants from both groups can not be found twice in a row for

monitoring per three days, (3) Participants from both groups giving birth during the study, (4) Participants from intervention group ever consume less than 4 Ajwa dates in one day, (5) Participants from control group ever consume Ajwa date (even one piece) in one day. The MDA measurements in both groups were performed before intervention and after the 8-week intervention period. Three milliliters of maternal venous blood samples were drawn from the median cubital vein and stored in a tube containing EDTA. The tube was then stored at a temperature of 4 $^{o}$C for a maximum of 30 minutes. The blood was then centrifuged at 3000 rpm for 10 minutes at 4 degrees Celcius ($^{o}$C). Blood plasma was separated and stored in a tube at -70 $^{o}$C before being examined in the laboratory. MDA levels were measured using a Spectrophotometric Assay. Briefly, thiobarbituric acid reacts with malondialdehyde to form a pink color, which is read at 532 nm using a spectrophotometer. All statistical analyses were carried out using SPSS 22.0 software. Continuous variables were reported as mean±SD and discrete variables as percent (%). MDA levels for the intervention group were compared with those of the control group using the Wilcoxon-signed rank test. A *p*-value less than 0.05 was regarded as statistically significant.

## RESULT

The baseline characteristics of the participants are presented in Table 1. Sample characteristics are displayed in the form of percentages and mean ± standard deviation, measurement results of MDA. MDA are displayed in the form of mean ± standard deviation. Results of MDA measurements on serum samples taken at the start of the study (Pre). In the intervention group, the maximum measurement result was 4.31, and the minimum was 3.21; the average value was 3.77 with a standard deviation of ± 0.41. In the control group, the maximum value was 4.31 and the minimum value was 3, the average value was 3.65 with a standard deviation of ± 0.44. The MDA levels in the intervention group were significantly decreased (p<0,001) following the 8-week intervention period, while in the control group, MDA levels increased slightly. In the intervention group (Post), the maximum measurement result was 3.5, and the minimum was 1.45; the average value was 2.15 with a standard deviation of ± 0.45. In the control group, the maximum value was 4.31, and the minimum value was 2.4; the average value was 3.75, with a standard deviation of ± 0.61. The study indicates the progressivity of preeclampsia was prevented in the intervention group but not in the control group. The intervention group showed a decrease in the median MDA value from 3.89 to 2.13. Meanwhile, the control group showed an increase in the median value from 3.65 to 4.1. Data show that in the intervention group, there was no progression of preeclampsia, whereas in the control group, there was a progression of preeclampsia (Figure 1).

## DISCUSSIONS

The seven Ajwa dates given in this study were equivalent to 50 to 60 grams. The part consumed in the flesh is 85 to 90 percent of the total weight. The current study revealed that the consumption of seven Ajwa dates daily can reduce MDA levels significantly. The effect of inhibiting the progression of the threat of preeclampsia can be seen from the decrease in the results of serum prooxidant marker measurements, which are predictors of the occurrence of preeclampsia. The effect of Ajwa dates is not

only as an antioxidant but also as a vasodilator and anti-inflammatory.

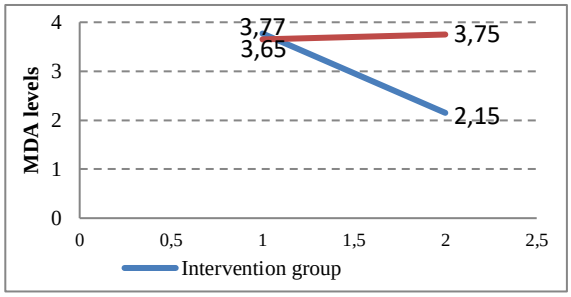


**Figure 1.** levels both groups

Table 1. The baseline characteristics of the participants

| Variables | Control group (n=10) | Intervention group (n=30) |
|---|---|---|
| Age (years) | 27,10 ± 6,69 | 27,77 ± 6,11 |
| Educational level | | |
| Primary school | 0 (0%) | 6 (20%) |
| Junior high school | 5 (50%) | 5 (16,7%) |
| Senior high school | 3 (30%) | 12 (40%) |
| Diploma | 0 (0%) | 4 (13,3%) |
| Bachelor | 2 (20%) | 3 (10%) |
| Gestational Age (weeks) | 22,02 ± 2,04 | 22,9 ± 2,95 |
| Gravid | | |
| 1st | 6 (54,5%) | 14 (46,7%) |
| 2nd | 2 (18,2%) | 7 (23,3%) |
| 3rd | 2 (18,2%) | 8 (26,7%) |
| 4th | 1 (9,1%) | 1 (3,3%) |
| Employment status | | |
| Employed | 7 (60%) | 21 (70%) |
| Unemployed | 3 (30%) | 9 (30%) |

First, Ajwa dates contain water-soluble antioxidants such as glutathione (GSH) and ascorbic acid. It also contains tocopherol, fat-soluble vitamins, and antioxidants. One gram of Ajwa dates contains GSH (0.062 µmol) with 86% redox status and ascorbic acid (0.051 µmol) with a redox status of 85.2%. The alpha, beta, gamma, and delta-tocopherol content in 100 grams of Ajwa dates are 0.212 ng, 0.022 ng, 0.22 ng, and 0.03 ng, respectively.[8]

Secondly, Ajwa dates contain some polyphenolic compounds, flavonoids, and phenolic acid, which play a role as an antioxidant. Flavonoids, which are mainly found within fruit skins, are the most abundant polyphenolic compounds found in Ajwa dates.[9] Flavonoids can be divided into various classes based on their molecular structure. The four main groups of flavonoids are flavones, flavanones, catechins, and anthocyanin. The total flavonoid content of Ajwa date fruit is around 2.79 mg/100 g. According to Hamad et al., concentrations of flavonoid compounds in 100 g Ajwa dates are mostly higher than in other dates.[8]

Lipid peroxidation is a common consequence of oxidative stress. Flavonoids protect lipids against oxidative damage by various mechanisms. First, flavonoids directly scavenging the free radicals,

resulting in a more stable, less-reactive radical.[10–12] Flavones and catechins are the most powerful radical scavengers among other flavonoids.[11] Second, flavonoids suppress ROS formation either by inhibition of enzymes or by chelating trace elements involved in free radical generation.[12] Flavonoids have chelating properties, which enable them to chelate/bind to metal ions in the human body to prevent them from being accessible for oxidation. Certain flavonoids have the potential capacity to chelate trace metal ions that play a vital role in oxygen metabolism and free radical formation.[13] Quercetin, in particular, is known for its iron-chelating and iron-stabilizing properties.[12] Flavonoids can also act as an intracellular antioxidant through inhibition of free radical generating enzymes such as xanthine oxidase, lipoxygenase, protein kinase C, cyclooxygenase, microsomal monooxygenase, mitochondrial succinoxidase, and NADPH oxidase.[12,14] Last, flavonoids can stimulate internal antioxidant enzymes.[14]

Ajwa dates also contain phenolic acid which content is varied according to the ripening stage.[15] Kimri stage (unripe) contain 290 mg phenolic/100 g dates, khalal stage (full-size, slightly crunchy, edible) contain 150 mg/100 g dates, rutab stage (ripe, soft, edible) contains 20 mg/100 g dates, and tamr stage (ripe, reduced moisture; edible) contains 10 mg/100 g dates.[9] The total phenolic content of Ajwa fruit varied between 245 and 455 mg/100 g.[15] The antioxidant mechanism of phenolic does not differ from that of flavonoids.[16]

In preeclampsia, the under-perfused placenta releases some factors such as pro-inflammatory cytokines, syncytiotrophoblast microparticles, angiogenic, and antiangiogenic factors into the maternal circulation causing diffuse endothelial cell dysfunction and increased systemic vascular resistance observed in the maternal syndrome.[17] Ajwa dates contain numerous minerals such as iron, zinc, copper, and calcium, whose concentrations are 0,15–0,5 mg, 0,46–0,52 mg, 0,37–0,5 mg, and 2 mg per 100 g flesh Ajwa dates, respectively.[15] Minerals have clinical antioxidant and anti-inflammatory properties that act on placental endothelial function, oxidative stress, and expression of angiogenic factors and thus contribute to trophoblastic invasion, spiral artery remodeling, and angiogenesis.[17] In this study, 7 Ajwa dates were equivalent to 60-80 grams, so it was suitable for the concentration to activate the process of preventing preeclampsia.

## CONCLUSION AND RECOMMENDATION

Consumption of seven Ajwa dates every day can reduce MDA levels significantly, and might be potential to inhibit the progression of preeclampsia in pregnant women.

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