Available online: http://journal.ipb.ac.id/index.php/jgizipangan ***J. Gizi Pangan, February 2021, 16(Supp.1):21-28***
Accredited based on DGHE, Republic of Indonesia No. 28/E/KPT/2019
ISSN 1978-1059 EISSN 2407-0920

Ajwa Date (*Phoenix dactylifera* L.) Juice for the Reduction of Gastric Damage on Wistar Rats

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ABSTRACT

The aim of this study was to analyze the effect of Ajwa date juice on the gastric damage of Wistar rats. This study was an experimental laboratory study with a posttest only control group design. Wistar rats were divided into five groups with five rats in each group (K, K+, P1, P2, and P3). The K group was given aspirin and no Ajwa date juice, K+ was given aspirin, while P1, P2, P3 were given aspirin and Ajwa date juice with concentrations of 20%, 40%, and 60%, respectively, for fourteen days. Gastric damage was viewed by microscope magnification of 400x and data was analyzed by the Kruskal Wallis and Post-Hoc Mann Whitney U test. The results showed that Ajwa date juice had a significant effect on reducing gastric damage with p=0.001. Ajwa date juice with a concentration of 60% was the most effective in reducing gastric damage in Wistar rats.

Keywords: aspirin, dates fruit, gastritis

INTRODUCTION

The stomach is an organ that can be easily injured due to daily intake and stress. Furthermore, an unhealthy lifestyle, environmental factors and over workload can also lead to an increase of gastric juice which can cause the gastric wall to peel off over time. Gastric mucosal damage occurs due to a mechanism that is not fully understood. An imbalance between invasive and defensive factors is caused by ulcerogenic agents which triggers gastric damage (Usman 2016). Increased gastric acid outside the normal limit will cause irritation and damage to the mucosal and submucosal lining of the stomach and if the increase in gastric acid is ignored, the gastric lining will be damaged or gastritis will be more severe (Tussakinah *et al.* 2018). Octaviana and Anam (2018) predict that if diseases are not taken seriously, the death rate caused by non-communicable diseases including gastric disease will reach 73% by 2020.

Countries with the highest incidence of gastritis are the United States (47%), India (43%), Indonesia (40.85%), Canada (35%), China (31%), France (29.5%), UK (22%), and Japan (14.5%) (Shalahuddin 2018). The number of cases of dyspepsia in the big cities of Indonesia is quite high. The incidence of dyspepsia in Jakarta is 50%, followed by Denpasar at 46%, Palembang 35.5%, Bandung 32.5%, Aceh 31.7%, Surabaya 31.2%, Pontianak 31.2%, and Medan 9.6% (MoH RI 2014).

Based on these cases, many studies have been aimed at finding ways to overcome this disease, both medically and naturally, by using natural food such as dates. Dates (*Phoenix dactylifera* L.) are a type of fruit that have many health benefits and has high nutritional value. Dates contain alkali salts and unsaturated fatty acids such as linoleic that act as gastro protectors (Baliga *et al.* 2011). In addition, dates contain flavonoid as an anti-inflammatory ingredient. Dates are a food that not only acts as a fruit, but also as a staple food (such as rice, wheat, et cetera) that can fulfill daily energy needs (Al-Alawi *et al.* 2017). A previous study by Musa *et al.* (2017) found that Ajwa dates can protect ulcers from ethanol in Wistar rats. This study was aimed to determine the effect of Ajwa date (*Phoenix dactylifera* L.) juice on gastric damage in aspirin-induced Wistar rats and to discover the difference of gastric damage among groups after protected by the Ajwa date (*Phoenix dactylifera* L.) juice.

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METHODS

Design, location, and time

This study was a true experimental research conducted in the laboratory. The researcher gave intervention to the subjects and observations were made to prove the effect of the intervention (Mentang *et al.* 2016). The research design used the posttest-only control group design. In this research, observations were only made once after treatment. The research was conducted at the Integrated Laboratory of the Faculty of Health Science of University of Darussalam Gontor, Mantingan Campus, Ngawi; the Center of Food and Nutrition Studies Laboratory at Gadjah Mada University (PSPG UGM); and at the laboratory of Pathology Anatomic, Faculty of Medicine, Public Health, and Nursing (FKKMK), Gadjah Mada University, Yogyakarta from 13th December 2019 until 21st January 2020.

This study has obtained ethical clearance from the Health Research Ethics Commission, Faculty of Medicine, University of Muhammadiyah Surakarta No. 2652/A.1/KEPK-FKUMS/XI/2019. The EC used animal study.

Materials and tools

The tools were five animal cages (each for five rats); Mettler Toledo brand analytic scales; IKA T-25 ULTRA-TURAX Digital High-Speed Homogenizer Systems; and experimental animal tools (scalpels, tweezers, Winomo's anatomical scissors). Tools for making histological preparations include one set of surgical instruments and object cups, tissue storage bottle containers, embedding cassettes, tissue paper, cotton wool, pan, oven, scalpel, and slide preparations. The tools used for HE coloring were staining jar, slide rack and glass cover. Furthermore, to observe the results of the study a light microscope and photo camera were used.

The subjects used in this research were 25 adult male white rats of the Wistar strain (Rattus norvegicus), aged 7–9 weeks with a mass of 150–200 g; test animal feed (Comfeed AD II standard feed and water); Ajwa dates (*Phoenix dactylifera* L.); aquades; and 80 mg aspirin. The Ajwa dates (*Phoenix dactylifera* L.) used were Al-Madina's Ajwa dates. Besides being high in vitamins and minerals, palm dates also contain 0.58% date fat, 23.09% total carbohydrates, and 4.08% protein (Daud & Abdullah 2019).

The materials used on the rats stomach after treatment and control were alcohol, xylol, formalin, paraffin, water bath, Harris Haematoxlin dyes, erosin, and canadian balm. Sample selection was performed using the simple random sampling method. The sample was divided into five groups with five rats in each group: K, K+, P1, P2, and P3. The number of experimental animals per group was calculated using the Federer formula (1967):

$$t\,(n-1)>15$$
$$5\,(n-1)>15$$
$$5n-5>15$$
$$5n>20$$
$$n>4$$
$$n=5$$

t: Total group
n: Total sample each group

Procedures

Determination of dosage

The dose of aspirin for adults weighing 70 kg is 5 g/day. Taking a daily dose of 4–5 g aspirin can cause gastric damage from mild dyspepsia, heartburn to gastric ulcer and duodenum in the first weeks of use (Brunton *et al.* 2018). On the other hand, Laurence and Bacharach (2013) found that the dose can only use the converse number, 0.018. Hence, the dose of aspirin given to rats weighing 200 g was 0.018 x 5,000 mg = 90 mg. The aspirin preparations used were one tablet having the weight of 80 mg, so the total was 22.5 tablets for all the 20 samples (4 intervention groups). The aspirin was crushed and dissolved in 20 ml of distilled water. One milliliter of the solution containing 90 mg of aspirin was given to each rat once a day and was given at an interval of one hour after consuming the Ajwa date juice.

According to previous research results, date juice was divided into three treatments with different concentrations of dates at 20%, 40%, and 60%. The results of this study were based on the use of three doses of date juice. The provision of the raw date juice was given orally to the rats at 2 ml of each concentration of date juice. In group P1, rats were given Ajwa date juice with a concentration of 20%, which means 0.4 g of dates were mixed with 2 ml aquades. Group P2 were given Ajwa date juice with a concentration of 40%, which means 0.8 g of dates mixed 2 ml aquades water. Meanwhile, group P3 was given

Ajwa date juice with a concentration of 60%, meaning that 1.2 g of dates were mixed with 2 ml aquades water. In this study, the dose given directly to each rat was 2 ml/200 g body weight orally every day for 14 days, arguing that the size of the gastric contents of rats of ±200 g weight was 3–5 ml. Ajwa date juice was given one hour before the aspirin.

The method of making the Ajwa date juice was as follows: first, the dates were separated from the date seeds. Then, the dates were weighed according to the doses before mixing them with 12 ml of water (for 6 rats). Finally, the mixture was blended with the IKA T-25 ULTRA-TURAX Digital High-Speed Homogenizer Systems.

Gastric histological observation

All rats were given anesthesia injections. Then a laparotomy was performed and the stomach was taken to make microscopic preparations. The gastric samples were fixed with 10% formalin. All samples were then sent to the Anatomic Pathology Laboratory, Faculty of Medicine, Gadjah Mada University for the manufacture of gastric microscopic preparations. The histopathological preparation method started from fixation, dehydration, clearing, embedding, and cutting. The samples were then finished with Hematoxylin-Eosin staining and mounting media and examined under a microscope with a magnification of 400x. The method used a double blinded procedure (Maria *et al.* 2017).

Data analysis

Based on the data, a statistical test was carried out on the hypothesis covering all aspects of this study to find out the differences in all groups through the Kruskal-Wallis H Test. Meanwhile, the Post-Hoc Mann-Whitney U Test was carried out to find out the average difference between the five groups. The hypothesis was declared meaningful or Ho was rejected if the result $p<0.05$ was obtained. This means that there was an effect of the giving of Ajwa date juice on gastric damage.

RESULTS AND DISCUSSION

The results obtained from the microscopic observation of the rats' stomachs are as follows:

Normal stomach. Microscopic Figure 1 (a) is a normal stomach and does not show any abnormalities. Normal stomachs were obtained in all rats of group K and three rats of group P3.

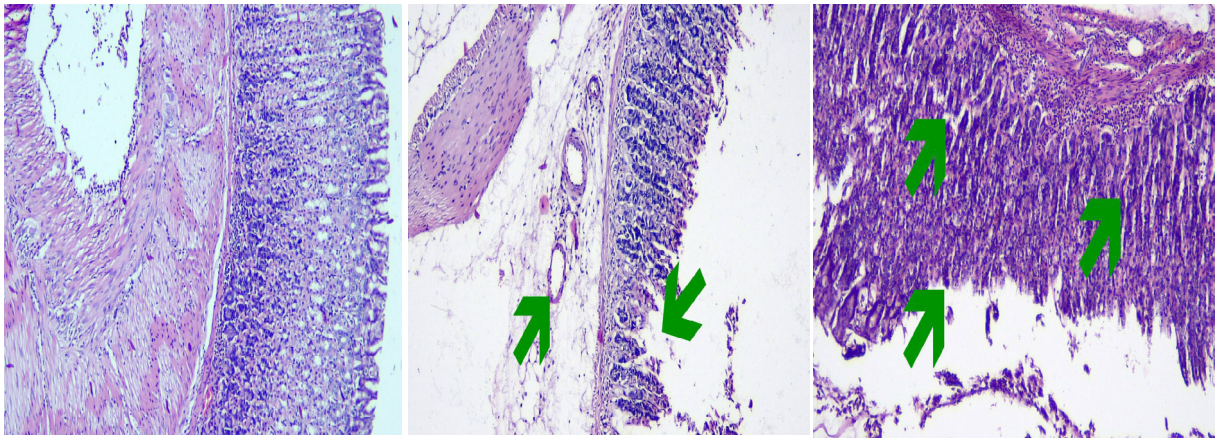
Mild level of gastric damage. Microscope Figure 1 (b) shows a mild level of gastric damage with signs of inflammation in the gastric mucosa and ulceration (green arrows). Mild levels of gastric damage was found in two rats of group P1, three rats of group P2, and two rats of group P3.

Severe level of gastric damage. Microscope Figure 1 (c) shows a severe level of gastric damage (green arrows) with signs of the inflammation of gastric mucosa. There were also signs of ulcers, namely the release of part of the mucosa (which involves the tissue under the epithelium) or the entire mucosa, and extravasation. Severe levels of gastric damage were obtained in all rats of group K+, three rats of group P1, and two rats of group P2.

Table 1 shows the difference between group K and group K+, which revealed a statistically significant difference ($p=0.001$). The results of the comparison between group K with the groups P1 and P2 also showed that there were significant differences. This is in contrast with the comparison between the group K and group P3, which showed a value of $p=0.134$ (there were no significant differences between the two groups). The results of the comparison of group K+ with treatment groups P1, P2, and P3 showed that Ajwa date juice had a protective effect on the stomach. The comparison of the p value of treatment groups P1 and P2 was not statistically significant ($p=0.549$), while the p value of treatment group P3 compared to groups P1 and P2 showed a significant difference ($p=0.031$).

The microscopic picture of group K shows normal gastric mucosa. This was because this group was only given feed and distilled water. Vascularity and the gastric barrier under normal circumstances were intended to protect the stomach (Mentang *et al.* 2016). To overcome or reduce the incidence of gastric disease, attention should be paid to food or things that cause and potentially cause gastric damage (Muhith & Siyoto 2016). It can be concluded that the health of the stomach will be maintained by consuming healthy and regular food and drink.

Statistically tested research data indicate that there were significant differences in the group K and the group K+ ($p=0.003$). This proves that aspirin was an aggressive factor of



(a) (b) (c)

Figure 1. (a) Microscopic picture of normal stomach; (b) Microscopic picture of mild level of gastric damage; (c): Microscopic picture of severe level of gastric damage

gastric damage as the theory outlined. Sari *et al.* (2020) state in their research that aspirin causes vasodilation. Aspirin or acetyl salicylic acid included in the salicylate group is a non-steroidal type anti-inflammatory drug or NSAIDs which is widely used in medicine for mild to moderate pain; it has antipyretic, anti-inflammatory and anti-coagulant effects. Several studies have used aspirin as a gastritis inducer ingredient in experimental animals. Aspirin works by inhibiting cyclooxygenase 1 and 2 enzymes so Prostaglandin (PG) levels decrease. Aspirin that is consumed orally results in increased gastric acid secretion and decreased gastric mucus secretion, which may cause irritation to the lining of the gastric mucosa. Aspirin causes the exfoliation of the epithelial cell surface and reduces mucus secretion, which is a protective barrier against acid. In addition, aspirin can suppress the production of prostaglandins and thromboxane (Mentang *et al.* 2016).

Rahmani *et al*. (2014) and Saleh *et al.* (2011) have proven that Ajwa dates can be used as an anti-inflammatory in inflammatory processes because it contains flavonoids that function as antioxidants. Antioxidants capture the free radicals (hydroxyl groups) in gastric damage caused by aspirin induction. The hydroxyl group of flavonoid compounds gives hydrogen atoms to free radicals so that it becomes stable and the process of gastric damage stops (Enola *et al.* 2018; Saafi *et al.* 2011). In addition, dates are rich in alkaline salts such as calcium, potassium, and sodium (Alghamdi *et al.* 2018). The mineral content (mg/100 g) of Ajwa dates (*Phoenix dactylifera* L) comprise of 187 mg calcium, 27 mg phosphorus, 476.3 mg potassium, 7.5 mg sodium, and 150 mg magnesium (Assirey 2015). Ajwa dates also contain unsaturated fatty acids, such as linoleic, which are the precursors of arachidonic acid (Ogungbenle 2011). Furthermore, arachidonic acid is converted into prostaglandins, where prostaglandin itself is an anti-inflammatory preparation (Jiang *et al.* 2019). This mechanism acts as a gastro protector preparation and can withstand the effects of aspirin and reduce gastric damage.

The Mann Whitney statistical test was performed to find out the difference between group K and group K+ and showed a statistically significant difference ($p=0.001$). This result shows that aspirin can cause gastric damage which in line with study by Seo *et al.* (2012). Hernandez *et al.* (2016) explained that aspirin, as shown by increased levels of p62 and ubiquitinated proteins and total LC3 and a decreased LC3-II/ LC3-I ratio, inhibited basal autophagy in the mucous membranes. Likewise, aspirin increased p62 and decreased the accumulation of LC3-II and the amount of puncta EmGFP/LC3B in AGS cells. The inhibition of autophagy enhances the vulnerability of gastric mucous. The comparison between group K with groups P1 and P2 revealed that there were significant differences. This means

Table 1. Comparison of gastric damage

		Damage level						p
		Normal (0)		Mild (1)		Severe (2)		
		n	%	n	%	n	%	
Group	K	5	100%	0	0%	0	0%	0.003
	K+	0	0%	0	0%	5	100%	
Group	K	5	100%	0	0%	0	0%	0.005
	P1	0	0%	2	20%	3	60%	
Group	K	5	100%	0	0%	0	0%	0.005
	P2	0	0%	3	60%	2	20%	
Group	K	5	100%	0	0%	0	0%	0.134
	P3	3	60%	2	20%	0	0%	
Group	K+	0	0%	0	0%	5	100%	0.050
	P1	0	0%	2	20%	3	60%	
Group	K+	0	0%	0	0%	5	100%	0.050
	P2	0	0%	2	20%	3	60%	
Group	K+	0	0%	0	0%	5	100%	0.005
	P3	3	60%	2	20%	0	0%	
Group	P1	0	0%	2	20%	3	60%	0.549
	P2	0	0%	3	60%	2	20%	
Group	P1	0	0%	2	20%	3	60%	0.031
	P3	3	60%	2	20%	0	0%	
Group	P2	0	0%	3	60%	2	20%	0.031
	P3	3	60%	2	20%	0	0%	

K: Was given aspirin and no ajwa date juice; K+: Was given aspirin; P1; P2; P3: Were given aspirin and ajwa date juice with concentrations of 20%; 40%; 60%

that Ajwa date juice with a concentration of 20% and 40% was unable to make the histological picture of the rat's stomach to become normal. In contrast, the comparison between group K and group P3 showed a value of p=0.134, meaning that there were no significant differences between the two groups. This means that Ajwa date juice with a concentration of 60% was very capable of making the histological picture of the rat's stomach normal. The comparison of the p-value of treatment groups P1 and P2 was not statistically significant; the increase in the dosage of Ajwa date juice did not have a statistically significant effect. The p-value of treatment group P3 compared to groups P1 and P2 showed a significant difference, thus the effect of Ajwa date juice differed statistically according to the dose. From the description above it can be concluded that increasing the dose of Ajwa date juice can significantly act as a gastro protector.

Ajwa dates were given to the P1 group for each rat at 0.4 g in 2 ml aquades. When converted to humans, the results obtained are 22.4 g of dates (without seeds) in 112 ml of water. The weight of a seedless Ajwa date is about 10 g, so 22.4 g of Ajwa dates amounted to approximately 2 or 3 pieces. Ajwa dates were given to the P2 group for each rat at 0.8 g in 2 ml aquades. When converted to humans, the results obtained are 44.8 g of dates (without seeds) in 112 ml of water. So, in this case, 44.8 g of Ajwa dates amounted to approximately 5 pieces. The Mann-Whitney statistical test between groups K and P3 showed no significant difference between the two groups. This means that the dose of Ajwa date juice at a concentration of 60% can make the histologic picture of the stomach normal as in the histologic picture of the stomachs of the K group. Ajwa dates were also given to the P3 group at 1.2 g in 2 ml aquades for each rat.

CONCLUSION

There was a protective effect from the Ajwa date juice (*Phoenix dactylifera* L.) on the gastric damage in Wistar rats. The best dose was Ajwa date juice with a concentration of 60% that could improve the histologic figure of the stomach to become normal or act as a gastro protector in Wistar rats.

Further research can be developed by providing a comparison between Ajwa date juice and medicines that protect the stomach. Thus, further study can be applied to study the effect it has on human stomachs directly.

ACKNOWLEDGEMENT

The authors would like to thank the Integrated Laboratory of the Faculty of Health Science of University of Darussalam Gontor, Mantingan Campus, Ngawi; the Center of Food and Nutrition Studies Laboratory at Gadjah Mada Univeristy (PSPG UGM); and the laboratory of Pathology Anatomic, Faculty of Medicine, Public Health, and Nursing (FKKMK), Gadjah Mada University, University of Darussalam Gontor for the access and technical support.

AUTHOR DISCLOSURES

The authors have no conflict of interest in this study.

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