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The Possible Antidiabetic Effect of *Ficus carica* L. Tablet on Iloxan-Induced Diabetes Model in Rats

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Abstract

BACKGROUND: Fig leaves are reported to have an effect on reducing blood glucose levels. However, the use of fresh leaves makes the effects obtained is not measurable and efficient.

AIM: The purpose of this research was to determine the antidiabetic potential of ethanol extract of fig leaves and to optimize tablet dosage formulations.

METHODS: Four tablet formulas were made using the wet granulation method. Formula I (FI), Formula I (FII), and Formula III (FIII) groups to give a tablet of ethanol extract of fig leaves with a dose of 40 mg, 60 mg, and 80 mg and placebo treatment group. There were eight groups of male rats strain Wistar treated as follows: Normal control, negative control, positive control (metformin tablets), basis group, placebo treatment group, F1, F2, and F3 groups. The antidiabetic activity was evaluated from a decrease in rat blood glucose levels. Previously, rats were induced first using alloxan 150 mg/kg intraperitoneally to damage β-pancreatic cells so that the rats could experience increased blood glucose levels. After giving treatment to each group for 14 days, a rat blood sample was then taken on days 9 and 14, which were then analyzed by the GOD PAP method with readings carried out using a spectrophotometer with a wavelength of 500 nm.

RESULTS: The average weight (mg) of FI tablets (617.8 ± 3.21%), FII (629.35 ± 8.16%), and FIII (643.6 ± 6.21%), and placebo tablet (666.45 ± 4.36%). As for the uniformity of size, all formulas have a diameter of 0.9 ± 0.0 (cm). For the hardness values of FI (5.7 kg), FII (1.31 kg), and FIII (3.09 kg), placebo tablet (2.98%). The value of friability FI (1.42%), FII (11.8%), and FIII (0.84%), placebo tablet (1.16%). While the disintegration time of FI (11.02 min), FII (10.10 min), and FIII (17.00 min), placebo tablet (12.23%). As for the uniformity of size, all formulas have a diameter of 0.9 ± 0.0 (cm). Whereas the dissolution rate (DE45) of each formulation decreased with increasing dose of extract, FI (73.73%), FII (74.80%), and FIII (69.80%). The treatment group of the ethanol extract of fig leaves at a dose of 40 mg, ethanol extract of fig leaves at a dose of 60 mg, and ethanol extract of fig leaves at a dose of 80 mg could reduce rats' blood glucose levels with statistically significant results ($p < 0.05$) compared to negative group. When it was compared to the positive group, it had significant results with a statistical value ($p < 0.05$).

CONCLUSION: Ethanol extract of fig leaf tablets had a significant effect on lowering rats' blood glucose levels.

Introduction

Diabetes mellitus is a metabolic system disorder characterized by an increase in glucose levels in the blood. Diabetes mellitus occurs as glucose is built up in the blood and fails to enter the cells. The failure is caused by the hormone insulin not functioning properly, or the amount is insufficient. The function of the insulin hormone is to help glucose enter cells [1]. Annually, WHO predicts an increase in diabetes mellitus sufferers. In 2040, the number of people with diabetes mellitus in Indonesia was predicted to reach 642 million [2]. With the high number of diabetes sufferers and the expensive treatment of the disease, it is necessary to have alternative therapies in herbal treatments that show good effectiveness and safety [3]. Fig plants are included in the mulberry (*Moraceae*) plant group. Fig leaves are one of 400 plants reported to be used as an antidiabetic. In tropical and subtropical areas, fig leaves are widespread, and it is reported that they have effectiveness as antidiabetic, antimicrobial, antipyretic, anti-cancer, antibacterial, and anti-inflammatory [4]. Boiled water and stew of fig leave methanol extract are reported to treat diabetes.

Fig leaves with the Latin name *Ficus carica* L. contain flavonoid compounds, β-sitosterol, and polyphenols reported to have antidiabetic effects [5]. More flavonoid content will be obtained using ethanol as a solvent compared to other solvents [6]. Various dose 100, 200, and 400 mg/kg body weight of extract were administered orally to the rats shown has no adverse effect on the liver or blood constituents and possess no hepatotoxic activity. [7]. Ethanol extract at a dose of 200 mg/kg body weight can affect the decrease in blood sugar and cholesterol in alloxan-induced male white mice, better than the dose of 100 and 300 mg/kg body weight and not significantly different compared to glibenclamide in reducing blood sugar levels of male white mice induced by alloxan [8]. Looking at the

problems and potential of fig leaves, it is necessary to conduct a study where fig leaves need to be formed in a tablet formulation as an alternative to diabetes treatment and can increase the therapeutic effect. It has prompted researchers to conduct research on the effects of fig leaves as an antidiabetic developed in tablet dosage forms. The choice of the *in vivo* method in this study was because we would like to identify the effect of giving fig leaves ethanol extract tablets to reduce rats' glucose levels in this study. The choice of tablet preparations is because tablet preparations are widely circulated in the community and easy to consume. It is expected that this research will be beneficial for the broader community with fewer side effects than using synthetic drugs.

Materials and Methods

Materials

The tools used in this study were analytical balances (Mettler Toledo), glassware (Iwaki Pyrex), microscope (Olympus), rat cage (size 50 cm × 30 cm), rotary evaporator (Erweka), water bath (Memmerth), sieve mesh number 14 and 16, oven, tablet printing machine, Semi-Automatic Hardness Tester Th 3b Copley, Friability Tester FR 2000 Copley, Disintegration Tester Erweka ZT X20, Spectrophotometer (Jasco).

Methods

Preparation and extraction of fig leaves

The simplicia determination of fig (*F. carica* L.) leaves was carried out at the Biology Laboratory, Faculty of Pharmacy, Ahmad Dahlan University (UAD). Simplicia fig leaves 710 gr were macerated using 70% ethanol with a 1part powder ratio dissolved with 10 parts solvent. The viscous extract obtained from the extraction process is calculated as the percent yield using the formula.

$$Yield\ value = \frac{Weight\ of\ viscous\ extract\ obtained}{Weight\ of\ simplicia\ powder} \times 100\%$$

Flavonoid compound test with thin layer chromatography (TLC)

Test for flavonoids and quercetin compounds used the TLC method with a GF 254 silica gel stationary phase and a mobile phase of ethyl acetate: methanol:water ratio of 6.5; 2.85; 3. Comparator standards used were a quercetin [9].

Tablets formulation

Tablets were prepared using the wet granulation method and the intraextra granular method in disintegrant use. Extracts of fig leaves, lactose, Sodium Starch Glycolate (SSG), and amprotab were mixed in a container until they turned homogeneous (mixture 1). Furthermore, PVP was prepared and then dissolved in boiling water little by little and mixed until it turned homogeneous. After the PVP dissolves, it was then added to mixture 1 gradually until the mixture 1 was wetted to form clenched granules. The granules were then sieved using a sieve number 14 (1410 microns) and then oven-dried at a temperature of 50□. Granules had been oven re-sifted using a sieve number 16 (1190 microns). Before mixing with the external phase, the obtained granules were subjected to an evaluation test first. After the granule evaluation test was carried out, the granules were mixed with magnesium stearate, talc, and SSG until they were homogeneous. When the granules were homogeneous with all formulas, they were ready to be molded into tablets. The formulation of each tablet is mentioned in Table 1 [10].

Table 1: Tablet formulation

	Placebo	FI	FII	FIII
Internal phase (94%)	Lactose monohidrat	40 mg Extract of fig leaves	60 mg Extract of fig leaves	80 mg Extract of fig leaves
	Lactose monohidrat	Lactose monohidrat	Lactose monohidrat	Lactose monohidrat
	SSG 2%	SSG 2%	SSG 2%	SSG 2%
	Amprotab 20%	Amprotab 20%	Amprotab 20%	Amprotab 20%
	Aquadest	Aquadest	Aquadest	Aquadest
	PVP 3%	PVP 3%	PVP 3%	PVP 3%
External phase (6%)	Talc 1.5%	Talc 1.5%	Talc 1.5%	Talc 1.5%
	Magnesium stearate 1.5%	Magnesium stearate 1.5%	Magnesium stearate 1.5%	Magnesium stearate 1.5%
	SSG 3%	SSG 3%	SSG 3%	SSG 3%

SSG: Sodium starch glycolate, FI: Formula I, FII: Formula II, FIII: Formula III.

Granule evaluation

Physical examination

The finished granules are seen in their shape and size. Good granules have a non-oval shape and are relatively the same size [11].

Granule compressibility test

Compressibility is the ability of granules to form tablets at a certain pressure. The finished granules are put in a special measuring cup to the stated volume. The greater the compressibility value of the granules, the less good the flow properties. The measurement used compressibility index with the equations:

$$\text{Compressibility index} : \frac{V0 - V1}{V1} \times 100\% \quad [11]$$

V0: volume of granules before treatment
V1: volume of granules after treatment

Moisture content

Moisture content test was carried out using the moisture balance method, a method that applies thermogravimetric with very high accuracy. Moisture analyzers use infrared or halogen as a heat source that will evaporate water in granules [11].

Tablet evaluation

Physical examination

Physical examination of the tablet is done by observing the tablet directly in terms of color, surface shape of the tablet and other physical disabilities [11].

Weight diversity test

Weight uniformity test is done by weighing 20 tablets carefully and calculating the average weight of each dose variation. Then weigh one tablet at a time from each dose variation [11].

Size uniformity test

This test is carried out using a caliper. A total of 20 tablets were measured in diameter and thickness using calipers and look for averages. Tablet diameters range from 4/3 to 3 times the thickness of the tablets [11].

Tablet hardness test

In the tablet hardness test, the Hardness Tester tool is used by as many as ten tablets placed on the test equipment one by one and the tool operated. The pressure results obtained are recorded from each tablet [11].

Friability test/tablet friability

In the tablet hardness test using a friability tool by 20 tablets was weighed and recorded by weight (W0). After that, 20 tablets were put into the device and operated for 4 min at a speed of 25 rpm or equivalent to 100 revolutions. After that, all tablets are removed and cleaned from existing fines and weighed (W1) [11].

Disintegration time test

The disintegration time test is carried out with a Disintegrator Tester by means of six tablets put in each basket, one basket containing one tablet. Previously, aquadest have been put in test containers and special tubes for baskets that have been heated to 37°C ± 2°C. After the tablet is inserted, then the basket is put in each tube and the appliance is operated for 15 min. After that, observe each tablet that is in each basket. If there are still one or two tablets that are not completely destroyed, then repeat the test [11].

Tablet dissolution test

In terms of the dissolution test, the standard curve was first determined. The standard curve determination for the dissolution test was carried out by dissolving the quercetin solution into ethanol with five different concentrations. This study used a concentration of 4 PPM, 8 PPM, 16 PPM, 20 PPM, and 24 PPM. The dissolved quercetin was then read for its absorbance using spectrophotometry with a wavelength of 435 nm [12]. After obtaining the absorbance of each concentration, the standard curve value was calculated. In this research, two dissolution tests were carried out: the S1 stage and the S2 stage because, at the S1 stage, the resulting dissolution test results did not meet the requirements. It was necessary to carry out the S2 dissolution test [11]. The dissolution test carried out in this study was a paddle dissolution test device with a speed of 50 rpm at a temperature of 37°C for 45 min, and every 5 min, a 5 ml solution was taken, which would later be analyzed by spectrophotometry with a wavelength of 435 nm [13]. In this research, the dissolution test passed the S2 stage.

In vivo test on antidiabetic tablet effect

This study was approved by the UMY Ethics Committee Number 051/EP-FKIK-UMY//II/2019. Rats used were 40 Wistar strains obtained from the Animal Laboratory of the Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta. The rats used are male sex, because if using female can be influenced by more hormones than male rats. Before being treated, for 7 days the rats were adapted to the new environment and given standard feed and *ad libitum* water. There were eight groups of Wistar rats that included three control groups, namely, one normal group, one positive control group with metformin administration, and one negative group with alloxan without a cure. The other five groups were the sample groups given CMC induction treatment, placebo tablets, Formula I (FI) tablets, Formula II (FII) tablets, and Formula III (FIII) tablets with each dose containing 40 mg, 60 mg, and 80 mg. In the previous study, a dose of 40 mg was able to reduce oxidative stress parameters in streptozotocin induced rats [14]. Rats were acclimatized before being treated. All groups were given alloxan at a 150 mg/kg dose to make the rats develop diabetes except the normal group. Before being induced by alloxan, the rats were fasted for 12 h and only given distilled water. After the alloxan induction, the rats were left for 3 days to wait for an increase in their blood glucose levels and then their blood sugar levels were checked. Rats were considered to be diabetic when

their blood sugar levels were above 140 mg/dl. Normal blood sugar levels of rats were 50–135 mg/dl. Rats with diabetes were given antidiabetic tablets for 14 days and were monitored for glucose levels on days 9 and 14.

Measurement of glucose levels in rats was carried out 4 times: First, before alloxan was induced to determine the initial value of glucose levels in rats, second on day 3 after alloxan induction to determine an increase in glucose levels in rats, and third and fourth were carried out respectively on the 9th and 14th day after being given therapy. The antidiabetic aimed to monitor the effects of the therapy that has been given. The calculation of serum blood glucose levels was determined by the GOD-PAP method. Blood was drawn from the retro orbital vein with a hematocrit pipette of ±1 ml. The blood that had been drawn was collected first and allowed to clot to separate the serum from the blood cells. Centrifugation was performed at a speed of 2500 rpm for 15–20 min; thus, the serum could separate completely. The separated serum was stored at a temperature of 2 −8□ so that the serum was not damaged. Each solution was then mixed and let it sit for 10 min at 37□ then the absorbance was read using a spectrophotometer with a wavelength of 500 nm, and the glucose level was calculated using the formula of GOD-PAP method [15].

In vivo test of tablets' antidiabetic effect was carried out by inducing tablets into rats using a sonde. Before giving to the rats, the tablets were dissolved first using 0.6% CMC. The function of CMC 0.6% is to make tablet into suspension preparations. The preparation of the suspension is done by first developing the CMC by leaving it in distilled water for 1 day. After the CMC solution is formed, mix with a tablet and crush until homogeneous then taken 2.5 mL of the suspension. Previously, the rats were induced with alloxan 150 mg/kg and waited for 3 days. The serum was then added with reagents, and the absorbance was read using spectrophotometry with a wavelength of 500 nm. Then, the results obtained were analyzed using the one-way ANOVA test [16].

Results

The determination results showed that the plants obtained were in accordance with the main ingredients used in this study, namely, fig plants with fig species (*F. carica* L) with the results are 1b-2b-3b-4b-12b-13b-14b-17b-18b-19b-20b-21b-22b-23b-24b-25b-800a-Moraceae 1a ficus-1b-16b-25b-40b-46a *F. carica* L. Maceration method was quite efficient as the yield obtained was quite good, amounting to 14.74%. The compounds that were bottled were fig leaves extract (a), quercetin compound (b), rutin compound (c), tablet FI (d), tablet FII (e), and tablet FIII (f). Based on the data obtained, the length of all samples was equivalent to quercetin's length at both 254 nm and 366 nm wavelengths. Thin-layer chromatography test are shown in Figure 1.

Granule evaluation

The water content of the granule was the water content in the granule. Placebo tablets contained 3.4% water content, FI tablets contained 3.53% water content, FII tablets contained 3.87% water content, and FIII tablets contained 3.89% water content. Based on the data obtained, all granule had met the moisture content test requirements, namely, below 10% for natural extract granule [10]. The moisture content would affect the process of pressing the tablet, tablet hardness, and tablet brittleness. The high-water content would cause the granule to be difficult to compress and less hard. Meanwhile, the small water content made the tablets easily brittle [17].

Compressibility test

Compressibility granule was the ability of the granule to flow when it would be printed into tablets. The greater the granules' compressibility value was, the less the granules' flow properties would be. Placebo tablets had a compressibility value of 12%; tablet FI had a compressibility value of 12%; tablet FII had a compressibility value of 8%, and tablet FIII had a compressibility value of 12%. Based on the data obtained, the placebo, FI and FIII granule composability values were classified as good because they had a granule compressibility value of 12% [18]. Meanwhile, the compressibility of granule FII was very good. It can be seen from the compressibility percentage of granule FII was below 10%.

Flow properties test

Flow properties are the ability of the granule to flow when it was printed. Flow properties can be determined by measuring the flowing time and angle of repose. The placebo tablet had a flow rate of 5 s; the FI tablet had a flow rate of 5.27; the FII tablet had a flow rate of 4.21; and the FIII tablet had a flow rate of 5.32. Based on the results of the data obtained, the granules' flow ability was classified as very good. It can be seen from the granule flow rate, which was below 10 s [19].

Evaluation of tablets

Physical Observation of Tablets: There were placebo tablets in this study, and three doses of fig leave ethanol extract used to make tablets, namely, 40 mg, 60 mg, and 80 mg. Each tablet had different characteristics. The tablet with higher dose of fig leaves

extract has be more smelled. The color of the tablets obtained from this formulation was green containing extracts. As for the placebo tablets, they were white.

Weight uniformity

Weight uniformity was evaluated by randomly weighing 20 tablets. The data obtained were calculated by calculating the average tablet weight divided by each tablet weight, and an absolute value was created and multiplied by 100%. Each formula's results should not have 2 tablets deviating more than 5% and no one tablet that deviated more than 10% [11]. The weight of the tablet desired in this study was 600 mg. The data obtained showed that the evaluation of weight uniformity in the four tablet formulas revealed very good results. The results are FI (617.8 ± 3.25% mg), FII (629.35 ± 1.25% mg), FIII (643.6 ± 3.16% mg), and placebo tablet (666.45 ± 1.31% mg). It can be seen in the data obtained that no more than two tablets deviated more than 5%, and no one tablet deviated more than 10%. The uniformity of tablet weight was influenced by the granules' flow properties and the granules' compressibility [20].

Tablet hardness

Tablet hardness test was carried out to assess tablets' resistance to shock pressure during and after tablets' manufacture. Tablet hardness was evaluated using a hardness tester as many as 10 tablets [11]. Tablet hardness significantly affected the brittleness of a tablet. The greater the hardness of the tablet was, the smaller the brittleness would be. The hardness of the tablet was greatly influenced by the level of pressure when printing the tablet. In other words, the higher the pressure was used, the harder the resulting tablet would be. The hardness values of FI (5.7 kg), FII (1.31 kg), and FIII (3.09 kg), placebo tablet (2.98%). Regarding the Placebo's hardness level, FII and FIII tablets did not meet the data's requirements. It could be seen in the data obtained showing that the three tablets had an average that did not enter the standard of tablet hardness, namely 4–8 kg [21]. While tablet FI had good hardness, it could be seen from the average hardness of tablet that FI was 5.7 included in the standard of tablet hardness.

Friability of tablets

The purpose of the tablet friability test was to determine tablets' resistance to shocks during the manufacturing, packaging, and distribution processes of tablets [11]. The requirement for the friability value of the tablet was <1%. The value of friability FI (1.42%), FII (11.8%), and FIII (0.84%), placebo tablet (1.16%). FI Based on the data obtained, t showed that the tablet friability value of each formula was different. The value of tablet friability was inversely proportional to the value of tablet hardness. The lower the tablet hardness value was, the higher the tablet friability value would be. It was because the tablet was getting stronger. The bond between particles would be stronger, so the tablet would not be easily brittle [22]. The tablets' brittleness was influenced by the tablets' hardness, the binder's concentration, and the concentration of disintegrant used. The lower the binder concentration was, the more brittle the tablet would be, and the lower the disintegrant concentration was, the less brittle the tablet would be. Thus, the tablets' friability was directly proportional to the binder's concentration and inversely proportional to the disintegrant concentration. In the data obtained, only FII tablets had good friability values. The value of the friability of the FII tablet had a friability value of below 1%. Meanwhile, in terms of the value of placebo, FI and FIII tablets had a friability value above 1%.

Disintegration time

Disintegration time is the time taken for the tablet to break down into particles. The factor that affected the disintegration time of tablet preparations was the pressure exerted when printing the tablets [11]. Tablets that were put under more pressure had a longer disintegration time because the tablet's hardness would inhibit the penetration of liquid into the tablet's pores. In addition, the concentration of the binder significantly affected the disintegration time. Too much binder or too little disintegrants would result in longer tablet breakdown times because the bonds between particles were too strong, so it took a longer time to dissolve [22]. The requirement for the disintegration of natural ingredients tablets was 30 min. Table placebo had a disintegration time value of 12:23 min; tablet FI had a disintegration time value of 11:02 min; tablet FII had a disintegration time value of 10:10 min; and tablet FIII had a disintegration time value of 17:00 min. Based on the data obtained, all tablets had a disintegration time that met the requirements, which was under 30 min because it used quite a lot of disintegrants excipients for the internal phase, namely, amprotab 20% and SSG 2% and, for the external phase, it used SSG 1.5% [10].

Dissolution

In this study, two dissolution tests were carried out, namely, the S1 stage and the S2 stage. This is because at the S1 stage the results of the dissolution test that does not meet the requirements, it is necessary to carry out an S2 dissolution test. The dissolution test was carried out in this study using a paddle dissolution test apparatus at a speed of 50 rpm at 37°C for 45 min and every 5 min a 5 ml solution was taken which would later be analyzed by spectrophotometry with a wavelength of 435 nm [13]. In this study, the dissolution test passed the S2 stage. The table of tablet absorbance test results is described in Table 2.

Table 2: Dissolution test

Tablet	Stage	Q	Q+5%	Q 12 tablet	Q-15
F1	S1	70.22	73.73	65.67	-
	S2	61.12	-		51.95
F2	S1	71.24	74.80	68.55	-
	S2	65.87	-		55.99
F3	S1	66.48	69.80	66.39	-
	S2	66.30	-		56.36

Table 3: Rats' blood glucose level (mg/dl)

Group	Blood glucose level (mg/dl)				
	Initials	9 days	14 days	Change in levels	% Change in levels
Normal	51 ± 4	61 ± 5	67 ± 4	16	31.1%
Negative	460 ± 35	520 ± 33	547 ± 33	87	18.9%
Positive	554 ± 47	390 ± 46	327 ± 46	−227	−40.9%
Placebo	452 ± 56	502 ± 53	538 ± 54	86	19%
Base	383 ± 78	431 ± 79	468 ± 79	85	22.1%
FI	535 ± 20	383 ± 20	350 ± 20	−173	−32.3%
FII	538 ± 15	354 ± 15	280 ± 15	−258	47.9%
FIII	553 ± 24	353 ± 24	266 ± 24	−287	51.8%

FI: Formula I, FII: Formula II, FIII: Formula III.

In vivo test on antidiabetic tablet effect

Rats with diabetes were given antidiabetic tablets for 14 days and glucose levels were monitored on days 9 and 14. Antidiabetic tablets used orally were metformin at a dose of 150 mg/kg body weight, ethanol extract tablets at a dose of 20 mg, 40 mg, and 60 mg and placebo tablets.

Measurement of rats glucose levels was carried out 4 times. First, before alloxan was induced to determine the initial value of glucose levels in rats, secondly on the 3rd day after alloxan induction to determine an increase in glucose levels in rats after alloxan was induced, the third and fourth were carried out respectively on the 9th and 14th days after being given therapy antidiabetic in order to monitor the effect of the therapy that has been given.

Discussion

The ethanol extract tablet formulation of fig leaves was carried out by wet granulation method. The first step is the phase weighing process in the formula. After the weighing process, the process of making the internal phase is carried out by mixing the ingredients in the form of ethanol extract of fig leaves, lactose, 2% SSG, and 20% amprotab until homogeneous (mixture 1) then carried out the dissolving process of PVP 3% into water at a temperature of 80°C. The process of dissolving PVP with water at a temperature of 80°C aims to dissolve PVP and also to prevent PVP from blowing faster than using 70% ethanol solvent. After PVP dissolves in air, then mix it with mixture 1 that was made previously. The mixing of PVP with mixture 1 aims to form bonds between particles so that they can be formed into granules [23].

After all the formulas have been mixed and homogeneous, the sieve is done with a mesh number 12 sieve. The purpose of sieving is to form the powder into granules and to accelerate the drying process. The wet granules that have been formed are then dried using an oven at a temperature of 50°C. Drying the granules aims to evaporate the water in the granules to obtain dry granules, so that it can facilitate the process of pressing the tablets. After obtaining the dry granule, the granule was then subjected to a second sieve with a mesh sieve number 16. This sieving aims to facilitate the process of pressing the tablets. The dried granules were then added with an external phase, namely SSG 3%, Mg Stearate 1.5% and Talc 1.5%. This mixing process aims to improve the smoothness of the granules when poured into the hoper, facilitate the tablet molding process and also increase the tablet disintegration time. After the external phase is added, tablet printing is carried out. The active substance used in this study was the ethanol extract of fig leaves with three different doses which were used as antidiabetic therapy in rats. Apart from the active substances, there are excipients that must be used in the manufacture of wet granulation method tablets, namely, fillers, disintegrants, binders, lubricants, and glidants. Fillers are used to give weight to the tablets and the one used in this study is lactose monohydrate. The disintegrants was used to increase the solubility of the tablets while in the stomach and in this study the disintegrants used were 2% SSG and 20% amprotab. The SSG used in this study was used in the internal and external phases, this is because the quercetin as active substances contained in fig leaves extract have a long disintegration time Quercetin being a flavonol belonging to Class II of BCS (Biopharmaceutical Classification) [24]. SSG is a super-disintegrant material which functions to increase the dissolution rate of drugs [25].

In the wet granulation method, an external phase is required in the form of glidants, lubricants and disintegrants. The glidan used in this study was talc 1.5%. Talc serves to increase the fluidity of the mass to be compressed by reducing friction between particles. Meanwhile, the lubricant used in this study was Mg stearate 1.5%. Mg stearate functions to reduce friction between the surface of the powder particles and the die walls during compression and ejection. In this research, disintegrants is used as an external phase; this is because the active substance has a low disintegration time [26]. Tablet are shown in Figure 2.

In the normal group, rats were not induced by alloxan, so that their glucose levels were not as high as those induced by alloxan. The purpose of holding the normal group was to determine the rats' normal condition for 14 days. The normal group experienced a change where it had an average blood level of 51 ± 4 mg/dl at the beginning of the study. After the 9th day, it became 61 ± 5 mg/dl, and on the 14th day, it became 67 ± 4 mg/dl. This is because the food given to the rats is A.D.II which contains 15% protein so that it slightly affects the glucose content in the rat's blood.

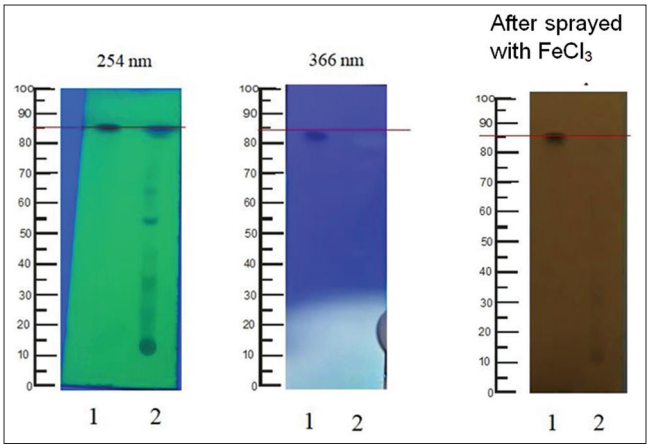

Figure 1: Thin-layer chromatography test with (a) standard compound quercetin, (b) ethanol extract of fig leaves

In the negative group, the rats still had diabetes from the beginning of the experiment to the end as they had been given alloxan before the initial blood draw. The negative group experienced a change where it had an average glucose level of 460 ± 35 mg/dl at the beginning of the study. After the 9th day, it became 520 ± 33 mg/dl, and on the 14th day, it became 547 ± 33 mg/dl. The increase in sugar levels occurred as the pancreas' function was not normal due to the induction of alloxan, which damaged the pancreas' beta cells so that insulin production was not normal, which caused an abnormal increase in glucose [27]. Results are shown in table 3.

In the positive group, the rats had diabetes at the beginning of the blood draw because alloxan was given before the initial blood draw. The purpose of holding the positive group was to determine the effect of metformin for 14 days. The positive group experienced a change where it had an average glucose level of 554 ± 47 mg/dl. After the 9th day, it became 390 ± 46 mg/dl, and on the 14th day, it became 327 ± 46 mg/dl. Metformin worked to reduce glucose levels by stimulating insulin secretion [28]. The placebo group experienced a change where it had a mean glucose level of 452 ± 56 mg/dl at the beginning of the study. After the 9th day, t became 502 ± 53 mg/dl, and on the 14th day, it became 508 ± 54 mg/dl. Placebo tablets did not contain compounds that could lower glucose levels, so placebo tablets could not reduce glucose levels.

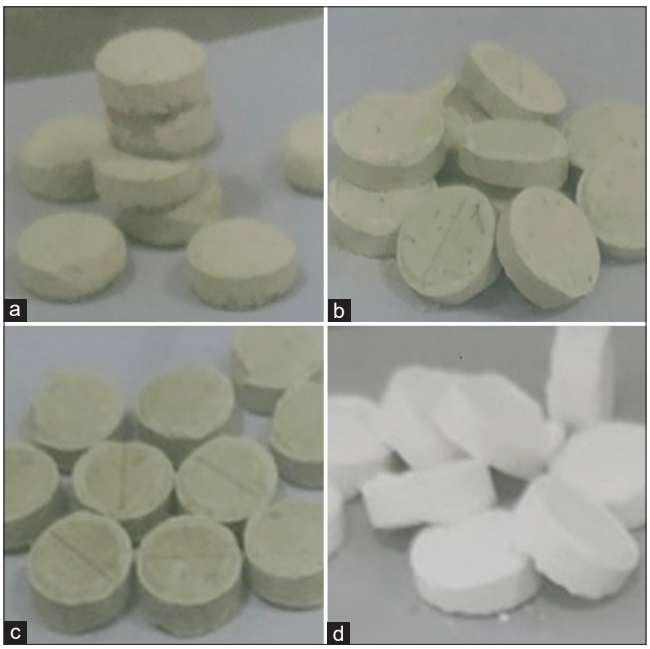

Figure 2: Tablet FI (a), Tablet FII (b), Tablet FIII (c), and Tablet Placebo (d). FI contains 40 mg of fig leaves extract, FII contains 60 mg of fig leaves extract, FIII contains 80 mg of fig leaves extract. FI: Formula I, FII: Formula II, FIII: Formula III

In the base group, the rats had diabetes at the beginning of the blood draw because alloxan was given before the initial blood draw. The aim of holding the base group was to determine CMC Na's effect when inducing tablets into rats for 14 days. The base group experienced a change, where at the beginning of the study, it had an average glucose level of 383 ± 78 mg/dl. After the 9th day, it became 431 ± 79 mg/dl, and on the 14th day, it became 438 ± 79 mg/dl. In CMC Na, which was used to make a suspension when induced to rats, it did not contain compounds that could reduce glucose levels. The highest ability to reduce glucose levels was tablet FIII compared to tablets FI and FII, which were significantly different because the FIII tablets contained more quercetin compounds than the FI and FII tablets. Whereas FII tablets had less quercetin compound compared to FIII and more than FI, so the ability of FII tablets to reduce glucose levels was not as good as FIII. Tablet FI had the lowest quercetin compound so that the ability to reduce glucose levels was lower than that of FII and FIII tablets and was significantly different that could be seen in the value ($p < 0.05$). Quercetin could reduce blood glucose levels by keeping pancreatic β cells working normally [29]. Treatment of quercetin has also shown to have ameliorative effects on type 2 diabetes in both *in vitro* and *in vivo* studies. Quercetin has been shown to effectively lower the plasma glucose levels and improve other diabetic-related parameters. The decreased levels of serum insulin in diabetic rats caused by the destruction of pancreatic β-cells were restored by quercetin treatments [30]. However, the actual mechanisms of these compounds are not fully understood.

Conclusion

The tablet formulation obtained to make ethanol extract tablets was to use the internal phase in the form of SSG 2% as a disintegrant, Amprotab 20% as a filler and disintegrant, PVP 3% as a binder with water solvent and filler in the form of lactose monohydrate and with an external phase in the form of talc 1.5% as a glidant, Mg stearate 1.5% as lubricant and SSG 3% as disintegrant. The ethanol extract of fig leaves had a significant effect

on reducing blood glucose levels of alloxan-induced rats. It could be seen from comparing the decrease in blood glucose levels in the FI, FII, and FIII groups compared with negative controls. The dose of fig leaves ethanol extract tablet had a significant effect at 80 mg/tablet. It could be seen from the comparison of changes in glucose levels in the FIII group with positive control. The FI and FII groups used the one-way ANOVA test with a value ($p < 0.05$). The dose of fig leaves ethanol extract tablets in FII and FIII groups had a higher effect than positive controls, which differed significantly. It could be seen from the comparison of the decrease in glucose levels in positive control with FII and FIII groups using the one-way ANOVA test with a value ($p < 0.05$).

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