Science and Technology Indonesia
e-ISSN:2580-4391 *p*-ISSN:2580-4405
Vol. 6, No. 4, October 2021

Research Paper

Formulation, Evaluation of Physical Properties, Anti-Cholesterol Activity from *Ficus carica* L. Leaves Extract Tablet

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Abstract
Figs knew playing vital roles in reducing cholesterol, strengthening the heart, and controlling respiration. Figs leaves extract with a dose of 50 mg/kg and 100 mg/kg can reduce triglyceride levels and can increase HDL cholesterol levels. This study aims to determine the effect of *Ficus carica* L. (fig) leaves extract on tablet dosage forms to reducing total cholesterol in rats induced with pork fat feed. Tablets were made by the wet granulation method in three formulas, there are F1 (extract dose 50 mg), F2 (extract dose 100 mg), and F3 (extract dose 150 mg), and compared with simvastatin tablets. The rats used in this study were 40 animals which were divided into 8 groups. Negative control group (induced of pork oil), F1 group, F2 group, F3 group, F4 group (placebo), positive control group (simvastatin 10 mg), base suspending agent group, and normal group.The average weight (mg) of F1 tablets (605.96 ± 9.94%), F2 (611.81 ± 12.33%), and F3 (639.09 ± 4.65%). As for the uniformity of size, all formulas have a diameter of 0.9 ± 0.0 (cm). for the hardness values of F1 (6.54 kg), F2 (5.31 kg), and F3 (5.43 kg). The value of friability F1 (0.8%), F2 (1.38%), and F3 (0.77%). While the disintegration time of F1 (13.31 minutes), F2 (19.48 minutes), and F3 (21.11 minutes). Whereas the dissolution rate (DE45) of each formulation decreased with increasing dose of extract, F1 (69.43%), F2 (64.95%), and F3 (60.04%). Extract contain quercetin as flavonoid, saponin, polyphenol, alkaloid, and tannin. Based on the results of statistical analysis, extract tablets did not differ significantly from simvastatin tablets in reducing total cholesterol levels. Tablet formulation of fig leaves extract with a dose variant has been shown to reduce total cholesterol in the blood between 18.3% until 37.98%.

Keywords
Fig Leaves, Tablets, Anti Cholesterols, Physical Properties, Formulation

Received: 21 May 2021, Accepted: 31 August 2021
https://doi.org/10.26554/sti.2021.6.4.285-295

1. INTRODUCTION

Hypercholesterolemia is one of the major modifiable risk factors for atherosclerotic cardiovascular disease (CVD), a global health problem, and is among the most common conditions encountered in the medical profession (Soran et al., 2018). Hypercholesterolemia is a condition where the cholesterol level exceeds normal which is >200 mg/dL. This happens because of the accumulation of cholesterol and lipids in the walls of blood vessels. The Joint British Societies (JBS2) guidelines recommend that optimal levels of plasma cholesterol should be ≤4 mmol/L or 154.68 mg/dL and LDL cholesterol ≤2 mmol/L or 77.34 mg/dL in patients with atherosclerosis or diabetes who have a combination of cardiovascular risk factors. Some influential risks such as smoking, increasing age, low glucose, HDL deficiency, and low socioeconomic classes (Bhatnagar et al., 2008).

One of the efforts to treat hypercholesterolemia is chemical drug therapy of the antihypercholesterol group. However, long-term use can cause serious side effects, such as the statin group, which can cause myopathy side effects. Nearly half of patients undergoing hypercholesterol therapy often forget to take one dose several times and think it does not affect their cholesterol levels. Therefore, the search for drugs made from natural ingredients to lower cholesterol in the blood as an alternative continues. One of the plants that can be used as an alternative in lowering cholesterol levels in the blood is fig leaves. Fig is considered very important to human beings by playing vital roles in reducing cholesterol, strengthening the heart, and controlling respiration. Over 100 bioactive compounds have been identified in figs such as arabinose, β-amyrins, β-carotenes, glycosides, β-sitosterols, and xanthotoxol. In vivo studies performed using fig extracts on HepG2 cells and showed reduced cholesterol levels. These properties make the hydro-extracts of fig leaves a potentially safe intervention to modulate postprandial hyperlipidemia (Gani et al., 2018). Based on previous research, fig leaf extract at a dose of 75 mg/kg, 150 mg/kg, and

a dose of 300 mg/kg was able to reduce total cholesterol in rats because it contains triterpenoid and flavonoid compounds that inhibit the HMK-CoA enzyme reductase. Figs leaves extract with a dose of 50 mg/kg and 100 mg/kg can reduce triglyceride levels and can increase HDL cholesterol levels (Joerin et al., 2014). Therefore, a formulation of fig leaves extracts tablets will be made that is beneficial in reducing cholesterol levels in the blood. Tablets have several advantages, namely having the least cost compared to other dosage forms, having ease in packing and distribution, the easiest preparations made for large scale production, and having a combination of chemical, mechanical and microbiological stability that is better than other oral forms such as syrup (Zaman, 2014). In this research, the formulation of foliar tablets is carried out with various doses to be given to rats that have been induced by high-fat feed, then cholesterol levels will be measured to find out how much cholesterol reduction by fig leaves.

2. EXPERIMENTAL SECTION

2.1 Materials

Pork oil as a high-fat feed, the ingredients for extracts consist of simplicia dried fig leaves obtained from the Zam-Zam Home Therapy, Yogyakarta, and 70% ethanol (Brataco®). Qualitative test materials consist of: Glacial acetic acid (PT. Brataco®), n-Butanol (PT. Brataco®), aquadest. The ingredients for making tablets include: thick fig leaves extract, lactose monohydrate (PT. Brataco®), magnesium stearate (Cv. Bratachem®), talcum (PT. Brataco®), amprotab® (Cv. Bratachem®), Sodium Starch Glycolate (Cv. Bratachem®), talcum (PT. Brataco®), amprotab® (Cv. Bratachem®), Sodium Starch Glycolate (Cv. Bratachem®), aquadest and PVP K-30 (PT. Brataco®). Other ingredients include: male white rat (*Ratus novergicus*) Wistar strain and Na-CMC (PT. Brataco®), standard feed, CHOD-PAP cholesterol reagent (DUMOLAB®), Glassware (IWAKI Pyrex®), waterbath (Memmert®), TLC Chamber (CAMAG®), analytical balance (Mettler Toledo®), oven (Memmerth®), tablet printing machine (Delta®), spectrophotometer UV-Vis (JASCO V-730®), centrifuge (EBA 20 Hettich®), tablet hardness tester (Th 3b Copley®), tablet friability tester (FR 2000 Copley®), tablet disintegration tester (Erweka Zt 222®), Tablet Dissolution Tester (Dis6000 Copley®).

2.2 Methods

2.2.1 Preparation and Extraction of Fig Leaves

The previously dried leaves of fig were subject to morphological examinations ranging from the smell, shape, and color of the leaves. After that, 1 kg of dried fig leaves is ground to form fig leaves powder. Then maceration using 70% ethanol with a ratio of 1:10 (1 kg of simplicia in 10 L of solvent). Maceration is done for 7 days by re-maceration in the first 5 days and continues again for 2 days with the remaining solvent. After everything has been filtered, the extract is mixed and evaporated in a rotary evaporator at 60°C until the solvent has partially evaporated. After that, the extract that has been evaporated is evaporated again in a water bath at 70°C until it becomes a thick extract.

2.2.2 Phytochemical Screening

Saponin test is carried out by testing the formation of foam in hot water after the drops of the reagent. As much as 1 drop of 2 N HCl is added to 1 g of the extract which is dissolved in hot water. If foam forms and lasts for five minutes or more, it shows that the sample contains saponin compounds (Harborne, 1996). An alkaloids test is done by adding a few mL of HCl to the 50 mg extract until it dissolves. Then the solution is tested by dripping two drops of three different reagents in different tubes, namely the recording of Mayer, Dragendorff, and Wagner. A positive reaction will be characterized by a yellowish or white precipitate in the Mayer reagent, an orange precipitate in the Dragendorff reagent, and a red-black color in the Wager reagent (Alasa et al., 2017). Anthraquinone test is carried out by boiling extract (300 mg) for 2 minutes with 0.5 N KOH (10 mL) and 1 mL hydrogen peroxide solution. Filtrate (5 mL) added acetic acid (10 drops) to pH 5 and toluene (10 mL). The top layer of the filtrate (5 mL) from shaking out plus KOH 0.5 N, if a red color appears in the water layer (base) indicates the presence of anthraquinone compounds (Harborne, 1996). The polyphenol test was carried out by heating the extract (300 mg) with water (10 mL) for 20 minutes in a boiling water bath. After cold, add $FeCl_3$ 3 drops. If the green blue formed indicates polyphenols (Harborne, 1996). Tannin test is done by 0.1 g of extract was dissolved in 10 mL distilled water and filtered and the filtrate was added with 5 mL iron(lll) chloride ($FeCl_3$) 1%. Positive reaction with the formation of dark blue or black (Harborne, 1996).

2.2.3 Flavonoid Compound Test with Thin Layer Chromatography (TLC)

Initial screening is done by testing the presence of flavonoid compounds using the Thin Layer Chromatography (TLC) method. Thin Layer Chromatography (TLC) is one of the simplest chromatogram methods and is usually used to analyze the presence or absence of a compound in a sample qualitatively by observing the color and value of Rf. In the TLC test, two phases are used, the mobile phase and the stationary phase. The stationary phase used was silica gel G60 F250 and the mobile phase used a BAA developer, namely n-butanol: glacial acetic acid: distilled water with a composition ratio of 4:1:5 and compared with the standard rutin (Anisa et al., 2018).

2.2.4 Wet Mixing and Granulation Stage

The ethanol extract of fig leaves was mixed with lactose and amprotab in a mortar until it was homogeneous (mixture 1). Then distilled water is heated until it reaches a temperature of 70-80°C, after heat PVP K-30 is added until dissolved and homogeneous while still stirring during the addition process. Homogeneous and soluble K-30 PVP solution is added to the mixture until everything is wetted while continuing to stir until it forms a mass that can be clenched. To find out whether

the mixture can be formed granules is by banana steak test, which is as much as one handgrip of the mixture in the head and then broken. If the mixture is broken completely without any mesh or residual powder falling, the mixture can be made granules with a defined sieve. After that, the mass is sifted with the mesh number 12 sieve. Then the formed granules are put into an oven at 50°C for about 40 minutes to dry. After the granules are dry, the granules are sieved by mesh number 16 and then an evaluation of the granules is carried out. The granule evaluation consists of a physical examination, humidity test, and compressibility index test.

Granule Evaluation

The finished granules are seen in their shape and size. Good granules have a non-oval shape and are relatively the same size (RI), 1995). 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. 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 (Kenkel, 2003). The test with a moisture analyzer takes about 3-15 minutes per sample (Rowe et al., 2009).

Phase Addition of The Outer Phase of The Granule

The dried granules are then added to the outer phase excipients namely magnesium stearate, talcum, and Sodium Starch Glycolate (SSG). Mixing granules with the outer phase is carried out in clear plastic and then shaken until homogeneous. The first step of mixing is to include SSG then mixed until homogeneous. After that add magnesium and talcum together and mix until homogeneous. When mixing with magnesium and talcum not too much, mixing is done a maximum of 3 minutes. Granules that have been given an outer phase are ready to be printed as many as 150 tablets for each formulation. After the tablet is printed, tablet evaluation is carried out namely tablet hardness, tablet hardness, tablet disintegration time, weight diversity, uniformity of size, and dissolution test of the tablet.

Tablet Evaluation

Physical examination of the tablet is done by observing the tablet directly in terms of color, the surface shape of the tablet, and other physical disabilities (RI), 2014). 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 (RI), 2014). Size uniformity 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 (Parikh, 2016). In the tablet hardness test, the Hardness Tester tool is used by as many as 10 tablets placed on the test equipment one by one and the tool operated. The pressure results obtained are recorded from each tablet (Parikh, 2016). In the tablet hardness test using a friability tool by 20 tablets were weighed and recorded by weight (W0). After that, 20 tablets were put into the device and operated for 4 minutes 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).

Disintegration Time Test

The disintegration time test is carried out with a Disintegrator Tester using 6 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 minutes. 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 (RI), 2014).

Tablet Dissolution Test

Dissolution testing is used to assess product stability and reproducibility so that product quality is maintained (Gravestock et al., 2011). Dissolution in oral preparations except for chewable tablets which have limited water solubility, dissolution values are more significant than when destroyed (RI), 2014). The dissolution test uses USP type 2 paddle-type basketball models by as many as 6 tablets tested separately in 900 mL volume of aquadest as media. Tablets that have been inserted, taken media solution every 5 minutes for 45 minutes as much as 5 mL. The amount of active drugs that can dissolve is calculated (Q) and expressed as a percentage (Anand et al., 2011). In addition to calculating dissolved drug levels, the DE45 value is also calculated to determine the number of dissolved substances and the dissolution rate of the drug seen in one time point (Oliveira et al., 2012).

2.2.5 Preparation and Treatment of Animal Test

The 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 females 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 libitium water. After the acclimation period, rats were divided into 8 treatment groups randomly, namely the normal group (B) which was only given normal food during the treatment, the suspending agent base group (NA) who were only given standard feed and 0.5% NaC CMC solution, the control group negative (KN) who were only given pig oil, positive control groups were given simvastatin (S), F1 Tablet group (50 mg extract tablet), F2 Tablet group (100 mg extract tablet), F3 tablet group (150 mg extract tablet), and the F4 tablet group (placebo). Each group consists of 5 rats. All groups on the first day after the acclimation period were given pork oil for the first 10 days except for the normal and base groups which were only given standard feed from the start.

Measurement of cholesterol levels was carried out 3 times, namely on the 0^{th} day, 10^{th} day, and 20^{th} day after the acclimation period. This research has been approved by The Health Research Ethics Committee of the Faculty of Medicine and Health Sciences Universitas Muhammadiyah Yogyakarta number 200/EP-FKIK-UMY/X/2019.

Induction of Fig Leaves Ethanol Extract Tablets in Test Animals

Tablets that have been made are dissolved with 0.5% CMC to become a suspension preparation. Then the suspension was induced to rats as much as 2 mL using NGT or gastric sonde every day. In the F1 group induced with a 50 mg tablet dose, the F2 group was induced with a 100 mg tablet dose and the F3 group was induced with a 150 mg tablet dose, and the placebo group was induced with the F4 tablet. Simvastatin dose of 10 mg is crushed then weighed according to calculations. Simvastatin powder was then dissolved with 0.5% CMC and induced as much as 2 mL to mice every day to the treatment group with gastric sonde or NGT.

Taking Blood Samples of Test Animals

Examination of rat blood samples was carried out 3 times, namely after the acclimation period (day 0) and subsequently on the 10^{th} and 20^{th} day after the acclimation period. Before drawing blood, rats should fast for 12-14 hours. Blood drawing is done through the eye vein. First, the rats are calmed first then they are pricked in the eye vein using capillary tubes. Absorb the dripping blood in the test tube and leave it for 15 minutes then centrifuged at 3000 rpm for 20 minutes. The obtained plasma is taken with a micropipette and put into an Effendort tube then stored at -20°C.

Examination of Total Blood Cholesterol Levels

Measurements were made using an enzymatic method, namely ELITech cholesterol reagents containing sodium cholic, 4-aminoantipirin, cholesterol esterase, cholesterol oxidase, buffer phenol, and peroxidase. 0.01 mL of blood plasma that has been taken is inserted into a test tube using a micropipette. Then 1 mL ELITech cholesterol reagent solution is added and leave it at room temperature for 20 minutes. The blanks used were 1 mL ELITech cholesterol reagent plus 0.01 mL aquadest, while the standard solution used 1 mL ELITech cholesterol reagent and 0.01 mL standard cholesterol. Plasma was measured for its absorbance with a UV-Visible spectrophotometer at a wavelength of 500 nm (Oliveira et al., 2009).

3. RESULTS AND DISCUSSION

3.1 Phytochemical Screening

In Table 1 based on phytochemical screening, extracts of fig leaves are proven to contain several secondary metabolite compounds namely flavonoids, alkaloids, saponins, tannins, polyphenols, rutin, and quercetin, but do not contain anthraquinone.

From Table 2 , in the thin layer chromatography test, number three showed that the fig leaves extract contained quercetin compound with an Rf value of 0.95. In Figure 1, it can also be seen that the quercetin compound has the same Rf value of 0.95. While the flavonoid compounds on the spot have an Rf value of 0.56. At 365 nm wavelength sightings, the extract did not show any clear spots that the extract contained flavonoids, but at wavelength sightings, 254 nm appeared to be vaguely found to be the same spots as flavonoid spots.

Table 1. Phytochemical Screening Fig Leaves Extract

Phytochemical Test	Observation	Result
Saponin	Formed 1 cm foam	Positive
Tannin	Black precipitates	Positive
Alkaloid	Brown precipitates	Positive
Anthraquinone	No change in color	Negative
Polyphenol	Greenish black coloration	Positive
Flavonoid	Yellowish red coloration	Positive
Rutin	Same spot color and Rf with standards	Positive
Quercetin	Same spot color and Rf with standards	Positive

Table 2. Results of Phytochemical Evaluation of Fig Leaves Extract

Parameter	Observations
Percentage yield	9.35%
pH	6.02
TLC	0.95

3.2 Tablet Formulation

The formulation of the tablet has been shown in Table 3. Figs leave extract tablet is made by wet granulation method, which is a method with the initial step of making granules which are mixed using solvent so it must be dried. The principle of the wet granulation method is the formation of granules so that it can improve the flow properties when pressing and the tablet size will be more uniform. In addition, wet granulation can reduce the loss of time in the process of making tablets.

The excipients used consisted of lactose monohydrate, Polyvinylpyrrolidone or PVP K-30, Sodium Starch Glycolate (SSG), Amylum pro tablet (Amprotab®), Magnesium stearate, and Talcum. The diluent or filler used is lactose monohydrate because it has better mixing results on tablets with the wet granulation method. In addition, lactose is recommended as a filler than others because it is more stable when mixed and has excellent flow properties (Huang, 2013; Niazi, 2009). Polyvinylpyrrolidone or PVP K-30 is used as a binding agent because it has more than 10% solubility in water. The solvent used is distilled water at 70°C to produce granules that have good flow properties, fewer fines, and better compressibility than using 96% ethanol. The concentration used as a binder is 3% in making fig leaves extract tablets. The concentration of PVP K-30 as a binder in the wet granulation method is 2-5%

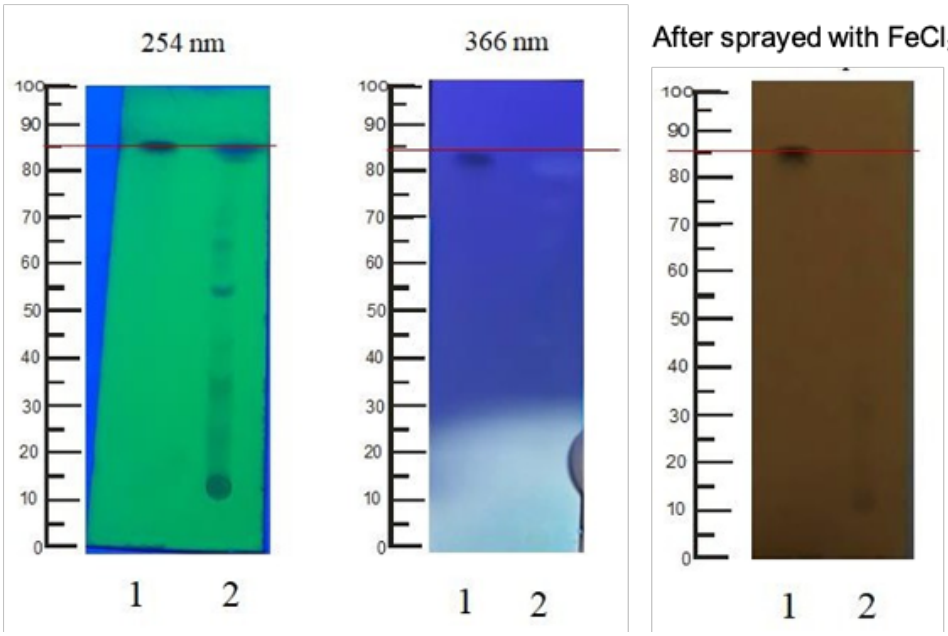

Figure 1. TLC Results

Table 3. Formulation of Tablets

Material	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
Figs leave extract	50	100	150	-
Lactose	364	314	264	414
Sodium starch glycolate (2%)	12	12	12	12
Amprotab® (20%)	120	120	120	120
PVP K30 (3%)	18	18	18	18
Aquadest	qs	qs	qs	qs
*Magnesium stearate (1.5%)	13.2	13.2	13.2	13.2
*Sodium starch glycolate (3%)	18	18	18	18
*Talcum (1.5%)	13.2	13.2	13.2	13.2

* external phase

so that the use of PVP K-30 in formulations is still acceptable. However, the disadvantage of using distilled water as a solvent is that the drying time is longer and the sugar compound in the extract can be dissolved in the distilled water (Niazi, 2009).

While the disintegrant materials used are Sodium Starch Glycolate (SSG) and Amprotab®. SSG was chosen because it can expand 7-12 times so that it helps the process of destruction of the tablet. In addition, SSG is not affected by the presence of hydrophobic materials (lubricant agents) and compress pressure in the disintegration process (Niazi, 2009). SSG is added in the outer and inner phases as much as 2% for the inner phase and 3% for the outer phase. The concentration is still in the range stated in the Handbook Pharmaceutical Excipient that the SSG concentration range is 2-8% with optimum use of 4%.

The use of extra-intra-granular disintegrant is more effective because it can break down tablets into more biodegradable granules thus accelerating the dissolution of drugs. The use of intra-granular disintegrants in wet granulation is ineffective compared to extra-granular because the disintegrated material will be wet and dry during the granulation process so that the crushing material will decompose partially and its activity decreases. SSG is one of the super disintegrants besides Croscarmellose sodium (CCS) and Crospovidone. Super disintegrant can accelerate disintegration time in just a few minutes and can increase dissolution from solid preparations. In addition, super disintegrant also provides better compressibility and compatibility values (Narang and Badawy, 2018).

In addition to using SSG as a disintegrant, the formula is also combined with Amprotab® by 20% in the inner phase. Amprotab® or starch pro tablet has a mechanism as a crushing agent with capillary action. Capillary action causes the liquid medium to penetrate the tablet so that the tablet will be destroyed, has various functions in the formulation namely as a diluent, binder, thickening agent, and disintegrant agent. The concentration of starch as a binder is 3-25% w/w. so the concentration used in the formula has entered the specified range (Niazi, 2009).

Magnesium stearate was chosen because it is more effective than water-soluble lubricants or other types of water-insoluble lubricants. Magnesium stearate is hydrophobic so that it can affect drug dissolution, causing the concentration of use and mixing time to be as low as possible. Meanwhile, if the amount and time of mixing of magnesium stearate are increasingly heavy, a thicker hydrophobic layer can be formed on the granules so that the tablet is more difficult to dissolve and can increase

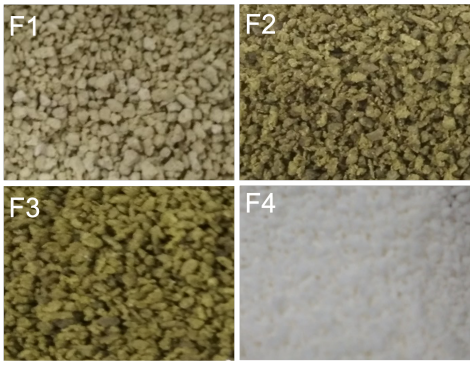

Figure 2. The Physical Appearance of Fig Leaves Extract Granules

the fragility of the tablet. The concentration range used in the formula is 1.5%, still entering the range of 0.25% -5% w/w as a lubricant (Niazi, 2009).

Talcum serves to improve the flow of granules in the hopper wall and reduce friction between particulates. The talcum concentration used is 1.5% as gluten in the formulation. A good talcum concentration to use as a glidant, as well as a lubricant, is between 1-10%. The combined outer phase between magnesium stearate and talc provides better flow properties and ease of printing than self-use. Talcum can function as gluten and lubricant, but its function as a lubricant is not good so it needs to be combined with good lubricants such as from the stearic group, namely magnesium stearate (Syofyan, 2015).

The granules of tablets that have been made are then evaluated by looking at the physical appearance, measuring the compressibility index, and the moisture content or LOD of each formula. The physical appearance test results of the granules can be seen in Figure 2. The physical appearance of the granules that the appearance of each formulation on average has around granule shape but with different sizes, some are slightly oval and round but irregular in shape. In formula 4 (F4) it appears that the granules formed are more oval or long. Whereas in formula 1 (F1) the same as Formula 2 (F2), the granules formed are mostly round but have varying sizes. Then, formulation 3 (F3) has a more diverse form of granules, which are round, oval, irregular, and have very diverse sizes. The difference in the shape of the granules produced is due to different dosages of the extract or active substance used. In addition to testing the fig leaves extract granules, placebo granules were also tested, which can be seen in Formula 4 (F4) that the granules obtained were mostly oval-shaped or slightly longer. The size of the granules is very diverse and has smaller size than the size of the extract granules. A good granule shape is spherical or round, but the effect of the granule shape on the tablet molding process is difficult to assess without a comparative measurement (Rowe et al., 2009).

Based on the evaluation results of the compressibility values in Tabel 4. The compressibility index and moisture content (LOD) test results show that the four formulations have an

Table 4. Physical Properties of Fig Extract Granules

Physical Properties of Granules	Formula			
	F1	F2	F3	F4
Compressibility index (%)	10	8	7	4
Moisture content (%)	4.48	3.96	3.18	3.4

excellent compressibility index of ≤10% based on Table 4. The Flowability scale is based on compressibility and the Hausner ratio. Compressibility value shows the value of a close relationship with the flow properties of granules, namely the compressibility value ≤10% has a Hausner ratio of 1.00-1.11 which means the flow properties of the granules are very good 25. The compressibility index determines how strong the granules can be compressed during printing, as well as to measure specific gravity, size, surface area, cohesiveness, compressed volume, and measure the flow properties of granules indirectly (Siregar and Wikarsa, 2010).

Figure 3. The Physical Appearance of Fig Leaves Extract Tablet

Determination of moisture content aims to determine the water content of the granules that have been made. Based on the evaluation of the four formulas the moisture content ranges from 3.18 to 4.38%, so it can be concluded that the moisture content of the four formulas has met the requirements. The water content requirement for extracts from natural ingredients is <10%. High water content can cause an increased risk of sticky tablets in the punch and die during the printing process, so they are prone to sticking (dan Makanan , BPOM).

Tablet evaluations included evaluating weight diversity, size uniformity, hardness, hardness, disintegration time, and tablet

dissolution. Tablet evaluation can measure the quality of the tablet by comparing the evaluation results with specified requirements. Physical observation of the tablet is done by visually observing the shape, color and detect any defects in the tablet.

In Figure 3. The physical appearance of the tablet, shows the four formulas have the same round shape. Formula F1 (fig 50 mg leaves extract) has less and brighter color and looks homogeneous. Whereas the F2 formulation (fig 100 mg leaves extract) has a more concentrated color than F1 and looks homogeneous. But in the formulation, F3 (150 mg fig leaves extract) has a very thick color than other formulas, and also the color is not homogeneous, there are some darker extract color spots. So, the higher the dosage of fig leaves extract used to produce tablets with increasingly dense and uneven colors.

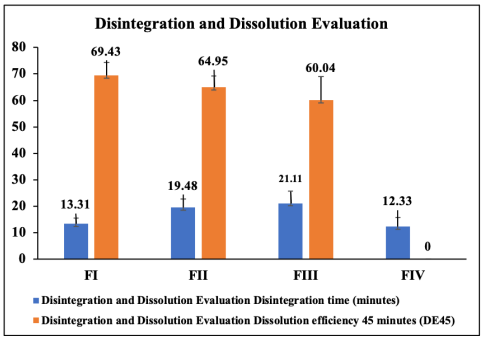

Figure 4. Physical Properties of Fig Leaves Extract Tablet

In Figure 4. The results of the diversity of tablet weights show the results of evaluating the diversity of tablet weights, of the four formulas fulfilling the requirements, none of the tablets have a diversity of >10% and no more than two tablets that have a weight variation of >5% (dan Makanan , BPOM). The diversity of weights can be influenced by the nature of the granule flow. Based on the results of the compressibility index evaluation has a pretty good value so that all four formulas have good weight diversity. From the results of the diversity of tablet weights, it can be seen that the average weight of tablets that have a similar size that does not stray far is formula 3 (F3). This can be influenced by the speed of the tablet machine being operated. The faster the machine, the granule filling on the die can be uneven. The results of uniformity of tablet size show the results of the evaluation of 20 tablets chosen randomly and measured the diameter and thickness using calipers, all four tablets have a uniform size. Punch stability when printing causes the tablet size to become uniform.

A tablet must have strength so that it does not crack or break easily but dissolves easily in digestion. The strength of a tablet is determined by measuring the hardness and hardness of a tablet. Tablet hardness was measured using a Hardness tester by measuring 20 tablets randomly. Conventional hardness requirements range from 4-8 kg. The results of the hardness test, friability, and disintegration time, that the four formulations have a hardness value that meets the requirements, which ranges from 5.31-6.45 kg. Evaluate the hardness of tablets to find out how influential the formulation of excipient material is on the disintegration time and the firmness or fragility of the tablets. The higher the hardness of the tablet, the longer the disintegration time, and the smaller the friability of the tablet. The hardness of the tablet can function to control the pressing strength of the punch during the printing process (in process control), if it turns out there is an increase or decrease in the hardness of the tablet, it means that the compressive strength of the punch changes. So that by monitoring the hardness value of the tablet, it can maintain the alignment of compression on the machine. The use of binder also affects the hardness of tablets, in the formula used PVP K-30 as much as 3% as a binder because PVP K-30 can form hydrogen bonds with active substances. PVP K-30 is dissolved in distilled water at 70-80°C to accelerate the dissolution of PVP K-30. The use of distilled water in PVP K-30 because in addition to PVP K-30 >10% solubility in water also because at the time of manufacture granules are not brittle quickly because water does not evaporate at room temperature. Different if dissolved in 96% ethanol will be more volatile during the process of making granules to produce brittle granules (Parikh, 2016).

In addition to the value of violence that affects the strength of a tablet, the value of violence is also very influential. The friability or fragility of the tablet is used to determine the tablet's ability to withstand shocks during the manufacturing, packaging, and distribution processes. The results of the test of hardness, friability, and disintegration time, showed that the four formulas have different values of friability. Formulas 1, 2, and 4 have a value of fierce <1% so they are eligible. For formula 2 containing fig leaves extract at a dose of 100 mg has a value of >1%. The hardness of the tablet can be affected by the hardness of the tablet, the harder the tablet is, the tablet is not easily brittle. In addition, the specificity of the tablet can be affected by the binding agent used.

Disintegration time presented the duration of the tablets melting in digestion. The longer the time the tablet is destroyed, the longer the effect tablet. The disintegration time of good natural ingredients tablets is no more than 30 minutes (dan Makanan , BPOM). In Figure 5, the results of the hardness, hardness, and time of disintegration test show that all four formulations meet the requirements of disintegration time. The increasing dose of extract, the longer the time for disintegrating tablets. The use of SSG (Sodium Starch Glycolate) can produce a faster disintegration time than amprotab® (Rohmani and Rosyanti, 2019). SSG has more hydrophilic substitution than its hydrophilic group, that the optimal strength of disintegration and dissolution than other starch derivatives (Dilebo and Gabriel, 2019).

The increasing dose of extract makes the disintegration time of tablets longer. Additives other than crushers are also affected by a lubricant which serves to reduce friction between the punch and dies so that the tablet easily comes out of the mold. The lubricant used is 1.5% magnesium stearate, magnesium stearate is hydrophobic and will form a layer on the

granules when mixing. It should be noted the amount and duration of magnesium stearate mixing. The more and the longer the mixing, the thicker the layer that surrounds the granule will affect the time of disintegration of the tablet because the nature of magnesium stearate is hydrophobic.

Dissolution rate is the speed of the drug to dissolve in the media, which can affect the intensity, duration of therapeutic response, onset, and bioavailability of the drug (Larson et al., 2010). Dissolution is done by taking six tablets randomly and tested using a type 2 Dissolution tester, which is the paddle type. Every 5 minutes the media is taken until the 45th minute. The active substance measured in this diss olution test is quercetin

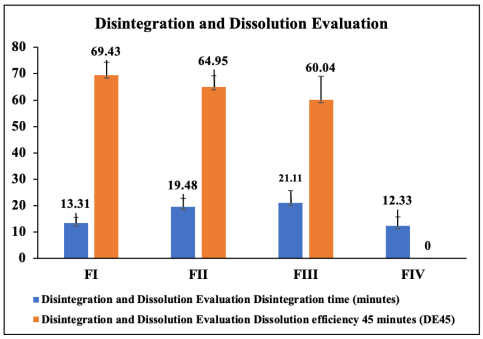

Figure 5. Disintegration and Dissolution Evaluation

which is one of the flavonoid compounds which has cholesterol-lowering benefits.

In Figure 5 dissolution of tablets, there is a Dissolution Efficiency 45 minutes (DE 45) value of all three fig leaves extract tablet formulations. In formulation 1 (F1) with a 50 mg extract dose has a dissolution rate value of 69.43%, while formulation 2 (F2) with a 100 mg extract dose has a DE45 value of 64.95%. Then for formulation 3 (F3) with 150 mg extract dose has a DE45 value of 60.04%. The higher the extract dose, the smaller the DE45 value, which indicates that the release of the drug is slower. The value of DE 45 is usually used to indicate the speed of a drug dissolved in the medium (Rohmani and Rosyanti, 2019). The solvent media used are aquadest and quercetin which have more soluble properties in non-polar solvents such as methanol. However, quercetin is found in O-glycoside (Oliveira et al., 2012). The presence of glycosides that are bound to quercetin makes it easy to dissolve in water and the dissolution media used is appropriate. The smaller the particle size of the drug, the dissolution rate increases because of the greater surface area. The smaller the time of disintegration of a tablet and the speed of dissolution of the drug because the tablet becomes faster into smaller particles. Quercetin being a flavanol belonging to class II of BCS (Biopharmaceutical Classification (Rao, 2020; Madaan et al., 2016).

3.3 Total Cholesterol Levels

In this study, there are five group criteria namely, positive control group, negative control, normal control, base control, and treatment group. The treatment group was divided into four groups, namely F1 (50 mg extract extract tablets), F2 (100 mg extract extract tablets), F3 (150 mg extract extract tablets) and F4 (placebo). Negative control was used to determine the effect of pig oil administration on total cholesterol levels without treatment. While the basic control serves to determine the effect of 0.5% Na CMC administration and normal control to determine the environment on cholesterol levels. A positive control is a control given simvastatin 10 mg after an induced fat diet for 10 days. Simvastatin is used to see the effect of clinically proven anti-cholesterol drugs. Before being given a fat diet, measured cholesterol levels on day 0 as a comparison after being given the first treatment. The high-fat feed used is 8 ml of pork oil every day for 10 days with a frequency of twice-daily administration. All groups were given except the normal group and the base group. After 10 days of the administration, blood is taken to measure cholesterol levels. After that, the treatment of fig leaves extracts tablets, placebo tablets, simvastatin tablets, and 0.5% CMC Na were given to each group for 10 days.

In this study, levels were measured using a spectrophotometer at a wavelength of 500 nm. Serum obtained from centrifugation of blood samples per rat at a speed of 3000 rpm for 20 minutes was reacted with ELITech cholesterol reagents so that enzymatic reactions occur. The reaction that occurs is the cholesterol ester in the serum will be hydrolyzed by the cholesterol esterase enzyme into fatty acids and free cholesterol. Then free cholesterol will be oxidized by the cholesterol oxidase enzyme into koles-4-en-3-one and hydrogen peroxide. Furthermore, this hydrogen peroxide will react with 4-aminoantipirin and phenol to be a red quinone-imine complex (Widada et al., 2016).

The data obtained can be seen in Figure 6, the average total cholesterol level, showing that after the treatment there was a decrease in the average total cholesterol level. Based on these data, rat's cholesterol levels after pork oil induction showed that average levels were still in the normal range. Normal levels of total cholesterol in rats are 40-130 mg/dL (Azhari, 2018). The increase in cholesterol levels after giving 8 mL of pork oil per day had a significant difference ($p < 0.05$), which means the administration of pig oil induction was able to increase total cholesterol levels. There is no increase in the average cholesterol level above normal. This can be influenced by the physiology of rats that cannot receive all the pork oil that is induced, even though it is divided into twice-daily administration. After induction of pork oil for 10 days, then each group was treated for 10 days. Based on Figure 6, the average total cholesterol level, all groups experienced a decrease in cholesterol levels. However, based on statistical test data the decrease in cholesterol levels between the positive group (simvastatin) with the treatment group that received extract tablets had a sig value >0.05. This indicates that the administration of fig leaves extract tablets is no more effective or nearly the same in reducing total cholesterol levels compared to simvastatin drugs. In Figure 6, dissolution of tablets shows DE 45 value of simvastatin tablets is greater than extract tablets, which is

82.91%.

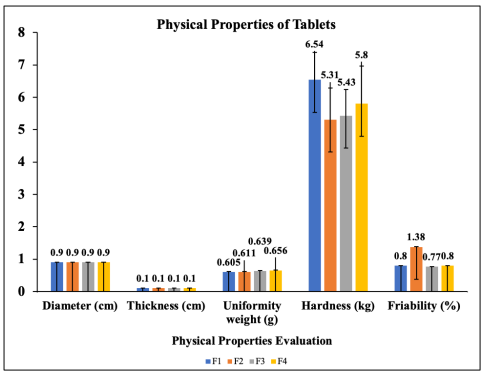

Figure 6. Cholesterol Level

Between figs leaves extract tablets (50 mg and 100 mg) had significant differences (sig <0.05). This explains that increasing the dose is directly proportional to increasing activity in reducing total cholesterol levels. But increasing the dose to 150 mg does not give a significant difference, which means that the extract tablet drug has reached saturated levels so that between a dose of 100 mg with 150 mg does not provide a significant difference in reducing total cholesterol levels. While between each group with the negative group gave a significant result (p <0.05), indicating that there was a difference between the negative group and all treatments. So that pork oil can increase total cholesterol levels in rats. It can also be seen in Figure 6, the percent decrease in total cholesterol levels, that the highest decrease was caused by simvastatin tablets by 54.18%. Whereas the most effective fig leaves extract tablet that can reduce total cholesterol levels compared to other extract tablets is a 100 mg dose tablet, able to reduce total cholesterol levels by 37.98%. If it is seen that a decrease in the 150 mg cholesterol level is no greater than a 100 mg dose. However, the reduction is still greater than the 50 mg dose of 25.94%.

Fig leaves have a variety of metabolite compounds such as flavonoids, tannins, alkaloids, saponins. These metabolite compounds that make fig leaves have a variety of effects on health. One of them can reduce total cholesterol in the body. Qualitatively, the phenolic compounds found in fig leaves consist of 3 hydroxycinnamic acids (3-and 5-O-caffeolyquinieacids and ferulic acid), one type of flavonoid glycoside (quercetin 3-O-rutinoside), and two types of furanocoumarins (psoralen and bergapten). It is proven that the fig leaves water extract contains quercetin 3-O-rutinoside more than other phenol compounds. About 42-87% contained quercetin 3-O-rutinoside from total phenols (Oliveira et al., 2012; Oliveira et al., 2009). Quercetin 3-O-rutinoside is one of the flavonoid compounds that are included in the flavonol members which are bound to sugar in their hydroxyl groups.

Flavonoids can reduce cholesterol levels by inhibiting the ACAT enzyme found in HepG2 cells and also the enzyme 3-hydroxy-3-methyl-glutaric-CoA reductase or more commonly known as the HMG CoA reductase enzyme. Both of these enzymes play a role in cholesterol synthesis, the ACAT enzyme will convert acetyl CoA from fatty acid oxidation reactions into HMG CoA which will then be reduced by the HMG KoA enzyme to mevalonate (Azhari, 2018). Flavonoid compounds in fig leaves are anthocyanin, flavonol, flavone, and biflavonil compounds. The mechanism of quercetin in reducing total cholesterol and LDL cholesterol is by inhibiting the secretion of Apo-B 100 in cells and can reduce MTP which plays a role in lipoprotein formation by catalyzing the transfer of lipids to Apo-B molecules. In addition to these mechanisms, quercetin can also inhibit the activity of the HMG-CoA reductase enzyme, which plays a role in cholesterol formation (Siregar and Wikarsa, 2010).

Cholesterol synthesis is influenced by several factors, one of which is the activity of HMG-CoA reductase. HMG-CoA reductase has a role as a cholesterol biosynthetic pathway in the liver by converting HMG CoA to mevalonate. Mevalonate is what will be converted into squalene lanosterol as a prototype of cholesterol. The HMG CoA enzyme is stimulated by the presence of thyroxine and insulin but is inhibited in the presence of glucagon. Therefore, why do people who have the habit of eating sweet foods have the potential to experience hypercholesterolemia (Yani, 2015). In this study, simvastatin was used as a positive control because it has the mechanism of inhibiting the enzyme HMG CoA reductase as well as the quercetin found in fig leaves extract. Simvastatin is proven to reduce cholesterols by inhibiting the activity of HMG-CoA. However, in response to the competitive inhibition of the enzyme an increase in the synthesis of the enzyme protein can overcome the competitive inhibition of the drug simvastatin Huggett et al. (1994). The characteristics of the formulations of each tablet give the results according to the requirements except the 100 mg dose extract tablet has the highest hardness above 1% and the lowest hardness value. Different dosages on tablets affect the dissolution rate of extract tablets. The higher the extract dose, the slower the dissolution rate (DE45). Fig leaves extract tablet (*Ficus Carica L.*) was proven to be able to reduce total cholesterol levels in rats induced with high-fat feed with pig oil. Tablet extract dose of 100 mg was higher in reducing total cholesterol (37.98%) than tablets with a dose of 50 mg (20.94%) with sig=0.006. Whereas the 150 mg tablet was not stronger in reducing total cholesterol (25.96%) compared to the 100 mg tablet (sig=0.367), but it was better than the 50 mg tablet (sig=0.03). The most effective dose to reduce total cholesterol in rats is a 100 mg tablet extract. Fig leaves extract tablets (*Ficus Carica L.*) were not significantly different from simvastatin tablets in reducing total cholesterol levels (sig=0.896). The effectiveness of fig leaves extracts tablets is almost the same as simvastatin tablets.

4. CONCLUSIONS

Tablet extract dose of 100 mg was higher in reducing total cholesterol (37.98%) than tablets with a dose of 50 mg (20.94%) with sig=0.006. Whereas the 150 mg tablet was not stronger in reducing total cholesterol (25.96%) compared to the 100

mg tablet (sig=0.367), but it was better than the 50 mg tablet (sig=0.03). The most effective dose to reduce total cholesterol in rats is a 100 mg tablet extract. Fig leaves extract tablets (*Ficus Carica L.*) were not significantly different from simvastatin tablets in reducing total cholesterol levels (sig=0.896). The effectiveness of fig leaves extracts tablets is almost the same as simvastatin tablets. Further stability test of the tablet is needed to determine the quality of the fig leaves tablets produced.

5. ACKNOWLEDGEMENT

This research was fully funded by Grant Research LP3M- Universitas Muhammadiyah Yogyakarta in 2019. The author is thankful to the School of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta for providing the facilities to carry out this research.

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