Science and Technology Indonesia
e-ISSN:2580-4391 *p*-ISSN:2580-4405
Vol. 8, No. 1, January 2023

Research Paper

Tablet Formulation with Galactomannan Binding Agent and Acute Toxicity Test from *Terminalia catappa* L.

Nilsya Febrika Zebua[1]*, Tandra Alexandro[1], Virda Widya Pratiwi[1], Syarifah Nadia[1], Supran Hidayat[1], Muflihah Fujiko[1], Muharni Saputri[1], Tedy Kurniawan Bakri[2], Nerdy[3]

[1]*Department of Pharmacy, Tjut Nyak Dhien University, Medan, 20123, Indonesia*
[2]*Department of Pharmacy, Syiah Kuala University, Banda Aceh, 23111, Indonesia*
[3]*Department of Pharmacy, Deli Husada Deli Tua Institut, Medan, 20355, Indonesia*
***Corresponding author**: nf.zebua@gmail.com

Abstract
Ketapang is one of the many medicinal plant species that grow in Indonesia and is used to treat various diseases. Ketapang leaves contain flavonoids, tannins, saponins, and terpenoids that have anti-inflammatory, antioxidant, antiviral, and antimicrobial properties. This study aimed to determine the LD50 and histopathology of Liver and kidney damage before the formulation of tablets containing galactomannan-binding agents. The toxicity determination method was carried out in vivo in experimental animals at doses of 4g/kg BW, 8g/kg BW and 16g/kg BW, and Liver and kidney histopathology was carried out before formulation into tablet preparations using the wet granulation method with various concentrations of binders and disintegrants, namely F1(8:0), F2(0:8), F3(4:4), F4(2:6), and F5(6:2). The results of the toxicity test showed an LD50 of 15.9959, liver damage at a dose of 4 g/kg BW hepatocyte karyorrhexis cells, central vein constriction, sinusoidal dilatation, a dose of 8 g/kg BW hepatocyte karyorrhexis, significant venous congestion, sinusoidal dilatation, a dose of 16 g/kg BW hepatocyte cells, karyolysis, dilated central veins, and dilated sinusoids. The results of the tablet mass preformulation test meet the requirements: the flow time test was 1.48-2.14 g/second, the angle of repose test was 24.60°-30.60°, and the tab index test was 5.33%-9.33%. The results of the tablet evaluation test were as follows: the tablet hardness test was 3.8-8.6 kg, the tablet friability test was 0.167-0.64%, and the tablet disintegration time test was 29.06-107.51 minutes.

Keywords
Ketapang Leaves, Toxicity, Histopathology, Tablets, Preformulation Test, Tablet Evaluation

Received: 26 August 2022, Accepted: 5 January 2023
https://doi.org/10.26554/sti.2023.8.1.129-136

1. INTRODUCTION

Excipients from natural sources have an advantage over synthetic excipients in that they are locally accessible, nonpolluting, biocompatible, and cheap as compared to imported synthetic products (Pawar and Geevarghese, 2013). Modifying natural polysaccharides is a new strategy for preparing environmentally friendly biomaterials. Polysaccharides are excellent alternatives to synthetic compounds for the manufacture of binders.

Galactomannan is a polysaccharide soluble in water, nontoxic, biocompatible, and economical. Galactomannan shows potential in the production field, and its application does not cause pollution; therefore, it does not disturb the ecosystem. In the pharmaceutical field, galactomannan is used as a suspending agent, emulsifier, and matrix in sustained-release tablets (Cerqueira et al., 2019).

Ketapang leaf is a medicinal plant that grows in Indonesia and is used to treat various diseases. Ketapang leaves possess anti-inflammatory, antibacterial, antioxidant, anticancer, and antidiabetic properties (Hayaza et al., 2019). However, its use in medicine is unknown due to its toxicity and safety. Therefore, it is necessary to test raw materials before they are formulated in pharmaceutical dosage forms.

Toxicity tests detect the degree of danger in biological systems exposed to humans. Doses that can cause toxic effects in humans are generally obtained from experiments using experimental animals that are carried out as supporting evidence for the safety of test preparations (BPOM RI, 2020). Organs that are susceptible to damage due to toxicity are the Liver and kidneys.

Tablets are solid dosage forms containing active substances with or without excipients (which improve the quality of tablet preparations, flow properties, and disintegration) made by compressing granules in a tablet machine (Departemen Kesehatan Republik Indonesia, 2020).

Herbal medicines have been gaining popularity. The thick extract of ketapang leaves is formulated in an oral dosage form, namely tablets, as it is a pharmaceutical preparation with excellent stability and is easy to consume and use.

Based on the description above, this research intends to formulate a binder derived from galactomannan, which is formulated with variations because, in general, herbal extracts tend to be hygroscopic, affecting tablet flow properties and can affect the compatibility of tablet preparations. Therefore, various binders were used to determine optimal tablet quality. In addition to testing the safety of the drug substance (*Terminalia catappa* L.) toxicity and the Liver's histopathology, kidney damage was assessed before formulation in tablet dosage form with galactomannan binding material.

2. EXPERIMENTAL SECTION

2.1 Materials

The ketapang leaf extract ingredients used in this study consisted of dried simplicia of ketapang leaves obtained from Medan Helvetia, North Sumatra and ethanol p.a. Qualitative test materials 96% ethanol, distilled water, hydrochloric acid, ammonia, diethylether, chloroform, lead(II) acetate, isopropanol, anhydrous sodium sulfate, methanol, anhydrous acetic acid, sulfuric acid, petroleum ether, iron(III) chloride, benzene, ethyl acetate, magnesium, sodium hydroxide, sodium carbonate, toluene, zinc, potassium dihydrogen phosphate, Bouchardart, Dragendorff, and Mayer. The ingredients for manufacture of the tablets included: ethanol extract of ketapang leaves, talc, mg stearate, starch, lactose, and galactomannan. Toxicity test materials included: male mice (Musmusculus), and Na.Cmc. Other ingredients in this study included: an analytical balance (AND®), oven (Memmert®), balance (Kenmaster®), rochefriabilator (Erweka®), hardnest tester (Erweka®), desintegration tester (Erweka®), index carr's (Erweka®), tablet press (Erweka®), hopper (Erweka®), water bath, mortar and stamper, mesh No. 14, stopwatch, litmus paper and filter paper.

2.2 Methods

2.3 Preparation and Extraction of Ketapang Leave

Extracts were made using the maceration method with 1000 g of p.a. ethanol as a solvent and with p.a. ethanol as a solvent. Maceration was carried out for three days while the extracts were stirred several times. The contents were stirred periodically, placed inside the bottle, and shaken to ensure complete extraction. Finally extraction process, the micelles were separated from the marc by filtration or decantation (Abubakar and Haque, 2020).

2.3.1 Phytochemical Screening

An alkaloid test was performed by adding HCl to the simplicia powder until the pH of the solution became acidic. It was then heated, cooled, and filtered. The filtrate obtained was divided into three tubes and drops of different reagents were added to each tube, namely Mayer, Bouchardart, and Dragendorf. A white precipitate indicated a positive reaction in the Mayer reagent, a brown residue in the Bouchardart reagent, and a brown residue in the Dragendorff reagent. The simplicia powder flavonoid test was conducted by adding methanol to the solution, refluxing for 30 min, and filtering. After cooling, kerosene ether was added, and two layers were formed. The bottom layer was evaporated at a temperature of 40°C, and the residue was dissolved in 5-10 mL of ethyl acetate and filtered. The filtrate was divided into two tubes: tube one was given Zn powder and 2N HCl and showed positive results if it showed an intense red colour. For tube 2, mg powder was added, and the concentrated HCl showed positive effects if a yellow to orange or a purplish red colour was formed. A simplicia powder saponin test was conducted by adding hot water and vigorously shaking the resulting solution. After shaking the solution, 2 N HCl was added, and a positive result was recorded if the foam persisted for 10 s. A simplicia powder tannin test was conducted in water, soaked for 30 min, and then filtered. The filtrate was then mixed with 5% iron (III) chloride, a positive reaction was recorded if the mixture turned green or blue-black, samples were treated with n-hexane for 2 h and filtered for the terpenoid and steroid tests. The filtrate was evaporated and subjected to the Liebermann-Burchard reagent. A positive reaction was recorded if a purple or red colour was formed, indicating the presence of a free triterpenoid compound group; if a green or blue to greenish blue colour occurred, it showed the presence of a free steroidal compound group (Doughari, 2012; Zohra et al., 2012).

2.3.2 Preparation and Treatment of Test Animals

The mice used were 16 male mice. Before being given the treatment, the mice were acclimatised to the new environment over seven days and given standard feed and water ad libitum during, before, and after the experiment (BPOM RI, 2020). After the acclimatisation period, the mice were divided into four groups that were randomly selected: the negative control group, which was given standard feed and Na CMC, and the treatment group F1 EEDKTP 4 g/kg BW, F2 EEDKTP 8 g/kg BW, and F3 EEDKTP 16 g/kg BW. Each group consisted of four mice. Guidelines for the care and use of laboratory animals documented by the Universitas Tjut Nyak Dien for the care and use of laboratory animals were strictly.

2.3.3 Toxicity Test

The test was carried out according to the guidelines (BPOM RI, 2020). The ethanol extract of ketapang leaves was given orally once for a 14-day test period, and then the mice were observed for any toxic symptoms that appeared. Observation times were 60 minutes, 90 minutes, 120 minutes, 150 minutes, 180 minutes, 210 minutes, and 240 minutes. The total observation time was four h periodically, which continued for the first 24 h, after which they were observed for 14th days. Particular attention was paid to the following areas: skin, hair, eyes, respiratory system, autonomic nervous system, central nervous system, somatomotor activity, and behaviour. On the 15th day, after 12 h of fasting, the mice were euthanised and

underwent surgery to remove the Liver and kidneys, which were taken and stored in 10% neutral buffered formalin for histological studies (Erhirhie et al., 2018; OECD, 2002).

Table 1. Toxicity Symptoms

Group	Toxic Symptom			
	Limp	Tremor	Diarrhoea	Walk with Stomach
Control	-	-	-	-
4 g/kg BW	+	-	-	-
8 g/kg BW	+	+	+	-
16 g/kg BW	+	+	+	+

Description: (+) contains compounds
(-) does not contain compounds

Table 2. Number of Deaths of Mice

Dosage of administration	Number of Mice	Number of Mice	
		Life	Death
Control	4	4	0
EEDKTP 4 g/kg BW		4	0
EEDKTP 8 g/kg BW		4	1
EEDKTP 16 g/kg BW		2	2

Table 3. Tablet Formulation

Ingredient	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
EEDK	40	40	40	40	40
Galactomannan	8	-	4	2	6
Starch	-	8	4	6	2
Talkum	1	1	1	1	1
Mg-Stearat	1	1	1	1	1
Lactose	Add 500	Add 500	Add 500	Add 500	Add 500

2.3.4 Making Galactomannan from Fronds

An amount of 1500 g of Arenga pinnata was cleaned, mashed with a blender for 3-5 minutes with the addition of 1:10 distilled water, and stored in a refrigerator for 24 h. Subsequently, a precipitate was formed using the filter. Ethanol (96%) was added to the precipitate at a volume ratio of 1:1 and the precipitate was stored in a refrigerator for 24 h. The formed precipitate was filtered through a white cloth and soaked in ethanol. The residue was filtered again and dried in a desiccator (Mirhosseini and Amid, 2012; Tamaki et al., 2010).

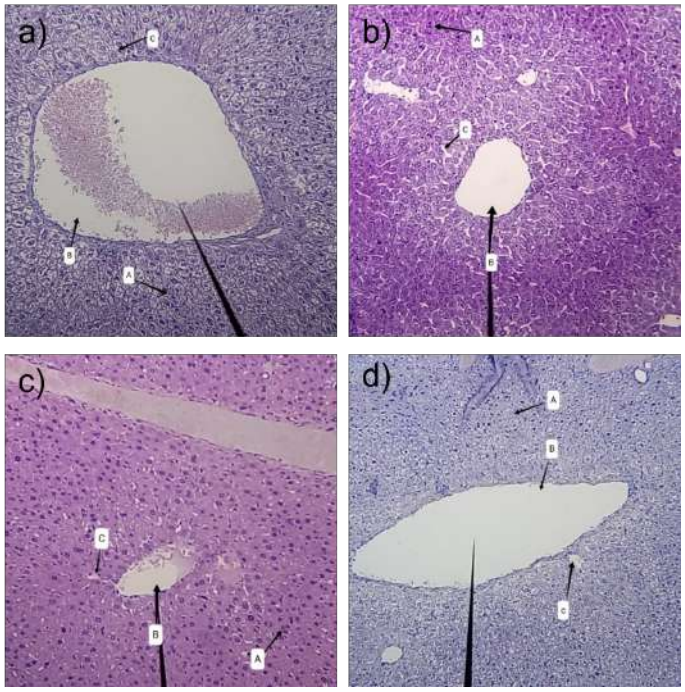

Figure 1. Liver Organs a)Na CMC 0,5%; b)EEDKTP 4 g/kgBB; c)EEDKTP 8 g/kgBB; and d)EEDKTP 16 g/kgB (Description: (A)Hepatocytes, (B)Central Vein, (C)Sinusoids)

2.3.5 Procedure for Making Tablets

The dried galactomannan powder was heated in a water bath, and hot water was gradually added to form a gel (mass 1). The extract was mixed with lactose until homogeneity, and the input of the disintegrant was ground to homogeneity (mass 2) by mixing mass one little by little into mass two until a paste-like mass was formed, then sieved with a mesh of 14. The resulting granules were dried at a temperature of ±50-60°C until a constant weight was achieved, and talc and mg stearate were added as lubricants. The resulting granules (Figure 3) were then tested for preformulation, including the flow time test; 100 g of granules were placed in a free flow, and the flow rate of the granules (requirements <10 s) was calculated. An angle-of-pose test is conducted. The angle of repose was obtained by measuring the diameter and height of the cone-shaped pile of granules (required for a grade of repose of $20° < \phi < 40°$), and the tap index test was carried out with a bulk density tester. In a measuring cup, some granules are inserted up to 50 mL, then tapped 20 times, and the volume was measured (Nnamani and Okonkwo, 2017; Lachman et al., 1994).

2.3.6 Evaluation of Tablets

The evaluation of tablet preparations includes organoleptic properties, weight uniformity, size uniformity, hardness, friability, and disintegration time (Lachman et al., 1994; Eisa et al., 2022). The fragility of the tablets was determined according to the Pharmacopoeia (2008), using a friability tester. Using a disintegration tester, the uniformity of weight and dis-

integration time was determined according to the Indonesian Pharmacopoeia (2020). Tablet hardness was measured according to United States Pharmacopeia (USP).

3. RESULT AND DISCUSSION

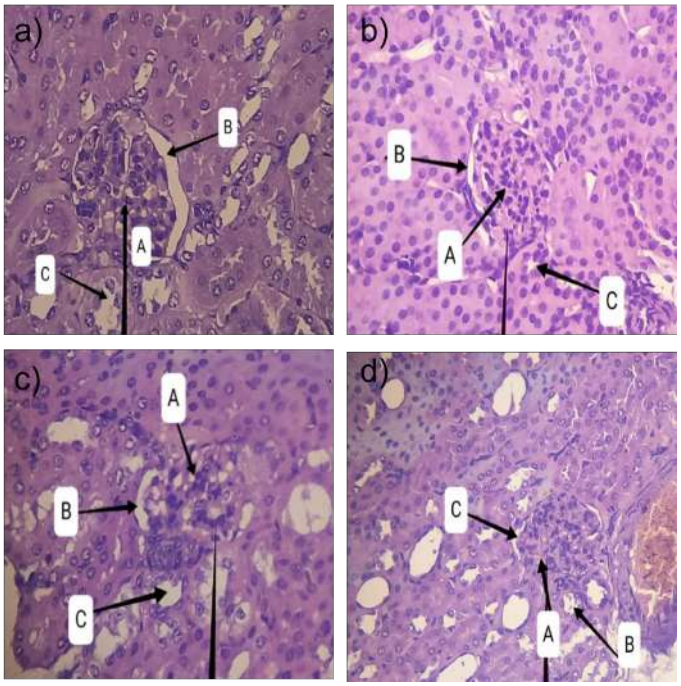

Figure 2. Kidney Organs a)Na CMC 0,5%; b)EEDKTP 4 g/kgBB; c)EEDKTP 8 g/kgBB; and d)EEDKTP 16 g/kgB (Description: (A)Glomerulus, (B)Bowman's Capsule, (C)Tubules)

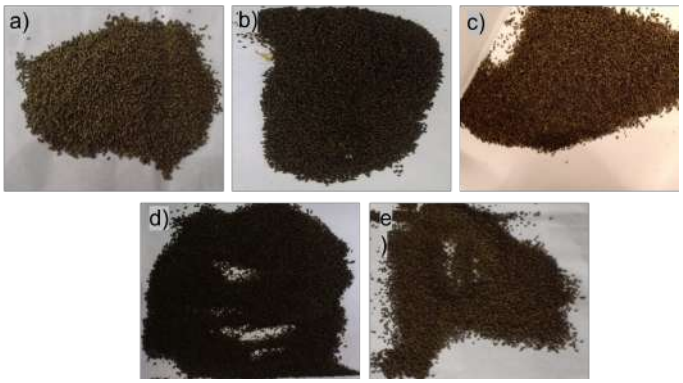

Figure 3. Granul of Tablet a)Formulation 1; b)Formulation 2; c)Formulation 3; d)Formulation 4; and e)Formulation 5

3.1 Investigating Phytochemicals

Results based on the phytochemical screening on the simplicia leaves of Ketapang showed that they contained alkaloids, flavonoids, saponins, tannins and steroids/triterpenoids.

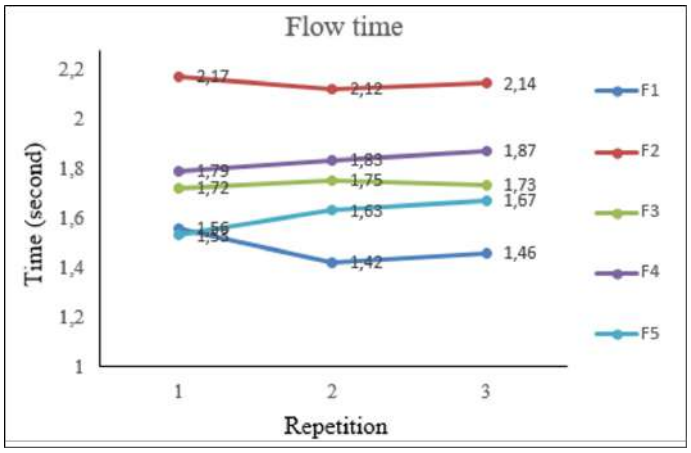

Figure 4. Flow Time

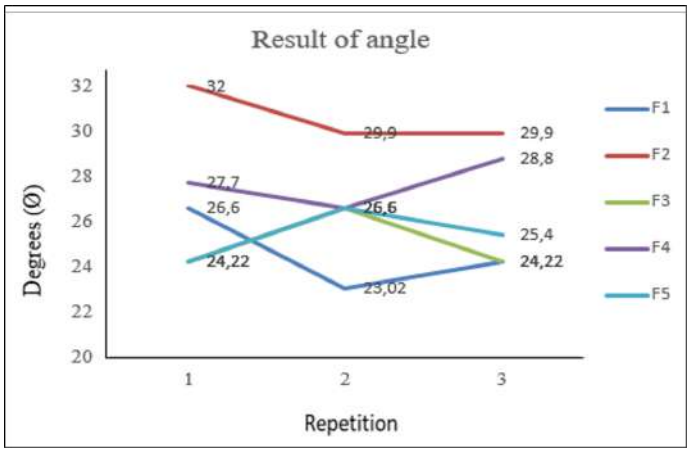

Figure 5. Still Angle

3.2 Toxicity Test

Based on the toxicity symptoms shown in Table 1, results were obtained at a dose of 4 g/kg BW. The toxicity test after the administration revealed a few signs of toxicity. Some mice experienced weakness: however, after two h, they returned to normal levels. This could be due to the fear experienced by mice when the extract was administered. At a dose of 8 g/kg BW, the mice experienced weakness, tremors, and a fast heartbeat, and the mice became lethargic and frequently fell asleep. It can be concluded that there were signs of toxicity at a dose of 8 g/kg BW. At a dose of 16 g/kg body weight, mice experienced decreased activity, weakness, tremors, diarrhoea, and a fast heart rate. Mice that died experienced restless behaviour, walking to and from, and convulsions before death. All groups with toxic symptoms appeared to depend on the concentration of the test preparation used. It was discovered that the higher the concentration of the test preparation, the greater the toxic symptoms are seen in the test animal (Hodgson and Levi, 1987; Sequeira-Cordero et al., 2019; Sharp et al., 2003).

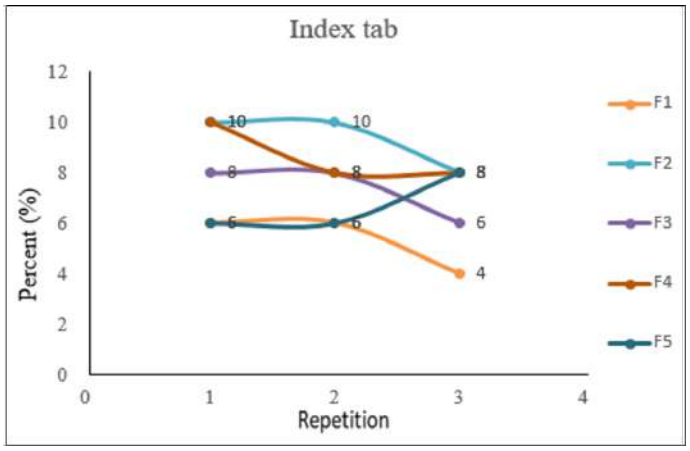

Figure 6. Index Tab

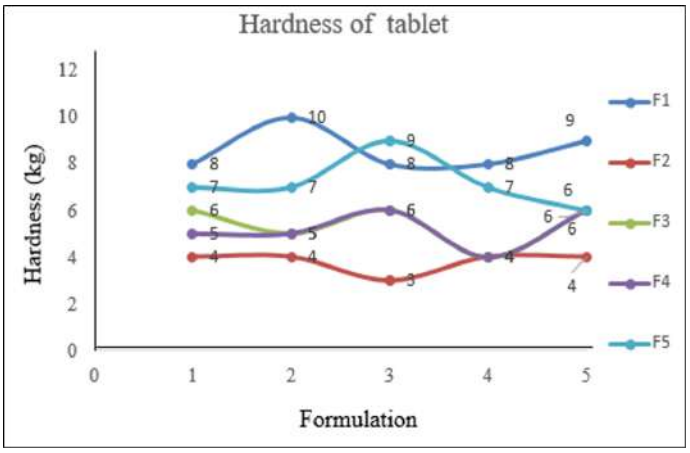

Figure 8. Hardness Tablet

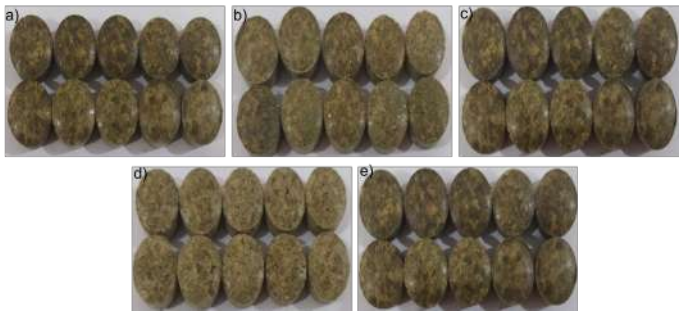

Figure 7. Result Tablet a)Formulation 1; b)Formulation 2; c)Formulation 3; d)Formulation 4; and e)Formulation 5

Table 4. Flow Time Test Results

Formulation	Flow Time (second)	Avarage (second)
F1	1.56 1.42 1.46	1.48
F2	2.17 2.12 2.14	2.14
F3	1.72 1.75 1.73	1.73
F4	1.79 1.83 1.87	1.83
F5	1.56 1.63 1.67	1.62

3.3 Observation of Mortality and Determination of LD_{50}

Based on the number of dead mice in Table 2, the LD_{50} value was 15.9959, and the ketapang leaf extract was categorised as practically non-toxic. An LD_{50} assessment can lead to the general conclusion that the lower the LD_{50} value, the more toxic the substance is being tested. Conversely, the higher the LD50 value is, the less likely it is to be harmful (Erhirhie et al., 2018). The phytochemical identification of the ethanol extract of Ketapang leaves showed that the ethanol extract contained phytochemicals such as alkaloids, flavonoids, tannins, saponins, and steroids/triterpenoids. These metabolites are used in various pharmaceutical and cosmetic preparations. The LD_{50} 15.9959 indicated that the ethanol extract of ketapang leaves was practically non-toxic (Erhirhie et al., 2018), indicating that these substances can be safely used in products such as drugs, nutraceuticals, and cosmeceuticals.

3.4 Results of Organ Macro Pathology Examination

Observations of the Liver and kidneys in all the groups showed no significant changes. A normal liver is a dark red colour; when pressed, it feels slightly hard and slippery. Mild liver degeneration does not affect the macroscopic appearance of the Liver because the Liver has a high regeneration capacity. Tissue damage due to toxic substances stimulates the mechanism by which liver cells begin to divide and continues until tissue mass repair is achieved. The abnormal kidney appears pale. On the surface structure of the irregular kidney nodules can be found (Andayani et al., 2018; Gasmi and Kleiner, 2020).

3.5 Hispathology Results in the Organs of Mice

Histopathology of the liver organs Figure 1. In the CMC Na 0.5% control group, histopathological images of the Liver were standard. The 4 g/kg BW EEDKTP treatment group experienced changes in hepatocyte karyogenesis and sinusoidal dilatation. The EEDKTP group of 8 g/kg BW observed karyoexic changes in hepatotic cells, central venous congestion, and sinusoidal dilatation. The 16 g/kg BW EEDKTP group experienced changes in hepatocyte karyolysis, major venous dilatation, and sinusoidal dilatation. Necrosis is the death of cells or tissues in living organisms, and as a result, these cells

Table 5. Results of Still Angle

Formulation	High (cm)	Diameter (cm)	Still Angle (⌀)	Average (⌀)
F1	2.0	8.0	26.60°	24.60
	1.7	8.0	23.02°	
	1.8	8.0	24.22°	
F2	2.5	8.0	32.00°	30.60
	2.3	8.0	29.90°	
	2.3	8.0	29.90°	
F3	1.8	8.0	24.22°	25.01
	2.0	8.0	26.60°	
	1.8	8.0	24.22°	
F4	2.1	8.0	27.70°	27.70
	2.0	8.0	26.60°	
	2.2	8.0	28.80°	
F5	1.8	8.0	24.22°	25.40
	2.0	8.0	26.66°	
	1.9	8.0	25.40°	

Table 6. Index Tab Test Results

Formulation	Pre Volume (mL)	Post Volume (mL)	Indeks Tap (%)	Average (%)
F1	50	47	6	5.33
	50	47	6	
	50	48	4	
F2	50	45	10	9.33
	50	45	10	
	50	46	8	
F3	50	46	8	7.33
	50	46	8	
	50	47	6	
F4	50	45	10	8.67
	50	46	8	
	50	46	8	
F5	50	47	6	6.67
	50	47	6	
	50	46	8	

can no longer function in taking nutrients because they have been damaged. The blackening of the tissue in histology preparations characterizes this.

Central vein congestion occurs because too much blood enters the arteries or too little blood enters the veins. Microscopically, congestion is characterised by dilatation of the arterial wall caused by a large blood volume in the central vein. The major vein dilates if there is damage because the endothelial cells lyse. A high compound concentration in the blood causes blood distribution with muscular perfusion to be channelled into the sinusoids, which causes the sinusoids to widen. Liver sinusoids function as a place for blood to flow which empties into the central vein, but some are inactive and serve as a blood reservoir (Saleh et al., 2017; Ta et al., 2013).

Results of histopathology of the kidneys organs Figure 2. In the control group, the CMC Na 0.5% of the kidneys were in average condition. The EEDKTP 4 g/kg BW, EEDKTP 8 g/kg BW, and EEDKTP 16 g/kg BW groups experienced glomerular hypertrophy and Bowman's capsule narrowing; in the 4 g/kg BW and 8 g/kg BW groups, the tubules were expected, but in the 16 g/kg BW treatment, the tubules were narrowed. Kidney damage is characterised by hypertrophy, atrophy, and hyperplasia. Several factors, including the entry of toxic substances, can cause kidney damage. Toxic substances can cause damage to the proximal tubular epithelium, narrowing the gap between the Bowman's capsule and the renal medulla, glomerular atrophy, and hypertrophy. Glomerular hypertrophy is tissue damage characterised by an increase in organ size due to an increase in the size of glomerular cells, which separates cells from one another. Glomerular hypertrophy is an early detection marker of kidney damage (Aslan et al., 2018; Ibrahim et al., 2018; Ho Kim et al., 2014).

3.6 Formulation Design

The design of the tablet formulas using galactomannan binders resulted in five formulas, as shown in Figure 7 and Table 3. Ketapang leaf extract tablets were prepared by the wet granulation method because of the consideration of extract characteristics, such as viscosity, hygroscopicity, flow properties, and powder comparability, so that the powder was easily compressed into tablet preparations.

The quality of all formulas can be determined from preformulation tests that meet the requirements. The pre-formulation test results are presented in Figures 4, 5, 6, and Tables 4, 5, 6 (Priya and Asuntha, 2022). In general, extracts tend to be more hygroscopic and have lower solubility. Therefore, good flow properties are the main specifications for achieving weight uniformity during tablet compression.

3.7 Fiscal Properties Tablets

Friability has been tested to assess the effect of shocks or shocks that often cause tablets to break or crack (Hoa et al., 2018). According to Lachman et al. (1994), a good value of 0.8% because of the lack of brittleness of the tablet indicates that the tablet has shock resistance that can maintain its shape. Based on Figure 9, formula 1 has a friability of 0.167%; formula 2 has a friability of 0.64%; and formulas 3, 4, and 5 have friabilities of 0.37%, 0.49%, and 0.19%, respectively. The fifth formula indicates that all the formulas satisfy the requirements. Subsequently, tablets were tested to assess their mechanical resistance during packaging and distribution. The varied galactomannan and starch components significantly increased the hardness and

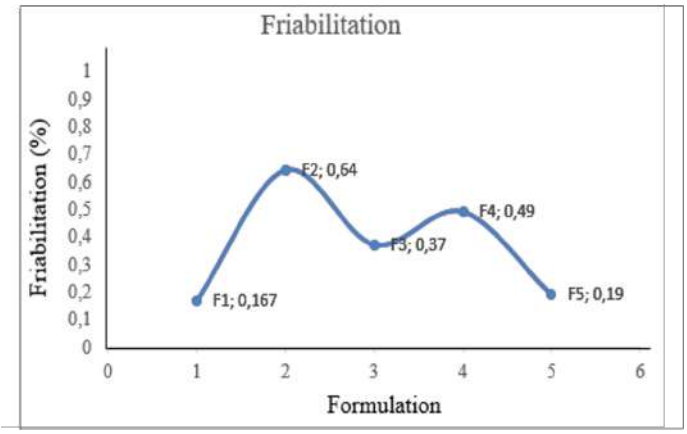

Figure 9. Friabilitation

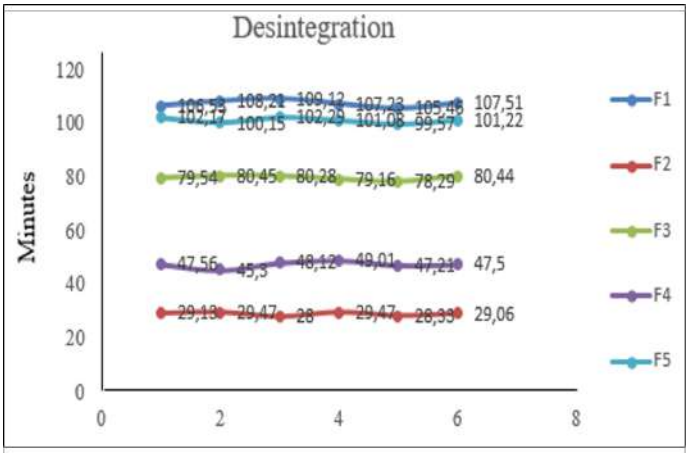

Figure 10. Disintegration

slowed the disintegration time (Lachman et al., 1994). Figure 8 shows that the tablet hardness values in formula 1 ranged from 8-10 kg, whereas in Formula 2, the tablet hardness ranged from 3-4 kg, in formulas 3,4 and 5 went from 4-6 kg, 4-6 kg, and 6-9 kg, from the 5^{th} formula only formulas 3 and 4 are eligible. The disintegration time was tested to assess the time taken by the tablet to break down and release the active substance. Based on Figure 10, it can be seen that the time needed in formula 1 is 105-109 minutes; in formula 2, the time required is 28-29 minutes; in Formulas 3, 4 and 5, the time required is 78-80 minutes, 45-49 minutes, and 100-102 minutes. Of the five formulas tested, they did not test formulas that meet the requirements of the Indonesian Pharmacopoeia in 2020. The disintegration time for ordinary tablets was less than 15 min. For tablets, the increase was not more than 60 min.

4. CONCLUSION

Toxicity testing of the Liver and kidney revealed damage and symptoms in mice. Ketapang leaf extract tablets met the requirements, variations in the concentration of binders and disintegrants significantly affect the physical properties of tablets, especially on the hardness and disintegration time; the higher the concentration of binders used, the more complex the tablets and the longer the disintegration time.

5. ACKNOWLEDGMENT

The authors thank the Faculty of the Pharmacy Department of Tjuk Nyak Dhien University for providing facilities to implement this research.

REFERENCES

Abubakar, A. R. and M. Haque (2020). Preparation of Medicinal Plants: Basic Extraction and Fractionation Procedures for Experimental Purposes. *Journal of Pharmacy & Bioallied Sciences*, **12**(1); 1–5

Andayani, N. K. P. S., I. Setyawati, and M. Joni (2018). Kidney Histopathology of *Gallus gallus domesticus* Infected by *E. coli* in Denpasar, Bali. *Advances in Tropical Biodiversity and Environmental Sciences*, **2**(1); 14–17

Aslan, A., M. C. van den Heuvel, C. A. Stegeman, E. R. Popa, A. M. Leliveld, G. Molema, J. G. Zijlstra, J. Moser, and M. van Meurs (2018). Kidney Histopathology in Lethal Human Sepsis. *Critical Care*, **22**(1); 1–12

BPOM RI (2020). Peraturan Badan Pengawas Obat Dan Makanan Tentang Pedoman Uji Toksisitas Praklinik Secara in Vivo. *Journal of Chemical Information and Modeling*, **53**(9); 21–25 (in Indonesia)

Cerqueira, M. A., A. C. Pinheiro, L. M. Pastrana, and A. A. Vicente (2019). Amphiphilic Modified Galactomannan as a Novel Potential Carrier for Hydrophobic Compounds. *Frontiers in Sustainable Food Systems*, **3**; 17

Departemen Kesehatan Republik Indonesia (2020). *Farmakope Indonesia Edisi VI*. Jakarta: Direktorat Jendral Bina Kefarmasian dan Alat Kesehatan Republik Indonesia (in Indonesia)

Doughari, J. H. (2012). *Phytochemicals: Extraction Methods, Basic Structures and Mode of Action as Potential Chemotherapeutic Agents*. INTECH Open Access Publisher Rijeka, Croatia

Eisa, A. M., N. A. El-Megrab, and H. M. El-Nahas (2022). Formulation and Evaluation of Fast Dissolving Tablets of Haloperidol Solid Dispersion. *Saudi Pharmaceutical Journal*, **30**(11); 1589–1602

Erhirhie, E. O., C. P. Ihekwereme, and E. E. Ilodigwe (2018). Advances in Acute Toxicity Testing: Strengths, Weaknesses and Regulatory Acceptance. *Interdisciplinary Toxicology*, **11**(1); 5–12

Gasmi, B. and D. E. Kleiner (2020). Liver Histology: Diagnostic and Prognostic Features. *Clinics in Liver Disease*, **24**(1); 61–74

Hayaza, S., S. Istiqomah, R. J. K. Susilo, B. Inayatillah, A. N. M. Ansori, D. Winarni, S. A. Husen, and W. Darmanto (2019). Antidiabetic Activity of Ketapang (*Terminalia catappa* L.) Leaves Extract in Streptozotocin-Induced Diabetic Mice. *Indian Veterinary Journal*, **96**(12); 11–13

Ho Kim, C., B. Jin Lim, Y. Sung Bae, Y. Eun Kwon, Y. Ly Kim, K. Heon Nam, K. Sook Park, S. Yeong An, H. Mo Koo, and F. Mee Doh (2014). Using the Oxford Classification of IgA Nephropathy to Predict Long-Term Outcomes of Henoch–Schönlein Purpura Nephritis in Adults. *Modern Pathology*, **27**(7); 972–982

Hoa, V. T., B. Huong, and N. D. H. Do Quang Duong (2018). Cause-Effect Relations and Optimization of Tablet Containing Eucommia Ulmoides and Gardenia Jasminoides Spray-Dried Extracts. *International Journal of Pharmacy and Pharmaceutical Sciences,*, **10**(7); 33

Hodgson, E. and P. E. Levi (1987). *A Textbook of Modern Toxicology*, volume 274. Elsevier New York

Ibrahim, K. E., M. G. Al-Mutary, A. O. Bakhiet, and H. A. Khan (2018). Histopathology of the Liver, Kidney, and Spleen of Mice Exposed to Gold Nanoparticles. *Molecules*, **23**(8); 1848

Lachman, L., H. A. Lieberman, and J. L. Kanig (1994). *Teori dan Praktek Farmasi Industri Edisi III*. Jakarta: Penerbit Universitas Andalas

Mirhosseini, H. and B. T. Amid (2012). A Review Study on Chemical Composition and Molecular Structure of Newly Plant Gum Exudates and Seed Gums. *Food Research International*, **46**(1); 387–398

Nnamani, N. D. and T. J. Okonkwo (2017). Optimization of Metronidazole Tablet Formulation Using *Manihot utilissima* Starch and a Combination of Processing Techniques. *Future Journal of Pharmaceutical Sciences*, **3**(1); 65–70

OECD (2002). *Test No. 423: Acute Oral Toxicity-Acute Toxic Class Method*. OECD Publishing

Pawar, H. and R. Geevarghese (2013). Development and Evaluation of Mucoadhesive Patch Using a Natural Polysaccharide Isolated from *Cordia dichotoma* Fruit. *Journal of Molecular Pharmaceutics & Organic Process Research*, **02**(03); 91–98

Pharmacopoeia, B. (2008). *British Pharmacopoeia Volume 1 & 2*. London: The British Pharmacopoeia Commission

Priya, N. L. and G. Asuntha (2022). Formulation and Evaluation of Sitagliptin Liposomes. *World Journal of Pharmaceutical Sciences*; 191–207

Saleh, R., B. H. Merghani, and W. Awadin (2017). Effect of High Fructose Administration on Histopathology of Kidney, Heart and Aorta of Rats. *Journal of Advanced Veterinary and Animal Research*, **4**(1); 71–79

Sequeira-Cordero, A., A. Salas-Bastos, J. Fornaguera, and J. Brenes (2019). Behavioural Characterisation of Chronic Unpredictable Stress Based on Ethologically Relevant Paradigms in Rats. *Scientific Reports*, **9**(1); 1–21

Sharp, J., T. Zammit, T. Azar, and D. Lawson (2003). Stress-Like Responses to Common Procedures in Individually and Group-Housed Female Rats. *Journal of the American Association for Laboratory Animal Science*, **42**(1); 9–18

Ta, W., A. Chawla, and J. Pollard (2013). Origins and Hallmarks of Macrophages: Development, Homeostasis, and Disease. *Nature*, **496**(7446); 445–455

Tamaki, Y., T. Teruya, and M. Tako (2010). The Chemical Structure of Galactomannan Isolated from Seeds of Delonix Regia. *Bioscience, Biotechnology, and Biochemistry*, **74**(5); 1110–1112

United States Pharmacopeia (USP) Convention (2009). *United States Pharmacopeia (USP) National Formulary 40 NF-35*

Zohra, S. F., B. Meriem, S. Samira, and M. Muneer (2012). Phytochemical Screening and Identification of Some Compounds from Mallow. *Journal of Natural Product and Plant Resources*, **2**(4); 512–516

