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Research Article

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Stability and Acute Toxicity (LD50) Test of Medicinal Filler made from Chicken Liver Supplemented with Silymarin

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ABSTRACT

Background: Chicken liver is a high-protein animal by-product with high palatability for carnivorous animals, particularly cats, making it a promising candidate as a natural medicinal filler. In veterinary pharmaceutics, palatability and safety are critical factors for oral dosage forms. Silymarin is a well-known hepatoprotective compound; however, its incorporation into animal-based fillers requires stability and safety evaluation.

Aims: to evaluate the stability and acute toxicity of chicken liver paste supplemented with silymarin as a potential medication filler for animals.

Methods: Stability tests were conducted on both chicken liver paste without silymarin and paste supplemented with silymarin. Evaluated parameters included organoleptic properties, homogeneity, pH, viscosity, adhesion, and spreadability. Acute toxicity testing (LD_{50}) was performed using twenty-five female rats divided into five groups. The control group received chicken liver paste without silymarin, while treatment groups received silymarin-supplemented paste at doses of 10, 15, and 20 g/kg body weight. Animals were observed for 14 days to assess mortality, clinical signs, body temperature, body weight changes, and hematological parameters.

Results: Stability testing demonstrated that both formulations met standard requirements across all evaluated parameters. No mortality or abnormal clinical signs were observed during the acute toxicity study. Additionally, body temperature, weight gain, and hematological profiles showed no significant differences between control and treatment groups.

Conclusion: Chicken liver paste supplemented with silymarin exhibited good stability and was classified as practically non-toxic, indicating its suitability as a safe and effective medicinal filler for animal use.

INTRODUCTION

The trend of keeping pets has increased worldwide in recent years. Pets, such as dogs and cats, are not only companions but also considered members of the family (Suchodolski 2024). While pets have been proven to provide many positive benefits, owning a pet also requires a significant responsibility and commitment to ensuring their well-being and health. This includes regular visits to the veterinarian for disease prevention and treatment.

Pet medications can be administered in various dosage forms such as tablets, liquids, capsules, powders, pastes, transdermal preparations, or injections. The most common type of medication administered to pets is the oral route. Oral administration tends to be easier in dogs than in cats. Research conducted by Sivén et al. (2017) showed that

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cats tend to refuse medication, with reactions such as spitting out the medication or excessive hypersalivation. One way to facilitate oral medication administration in cats is to ensure the medication suits their preferences. Cats' preferences relate to taste, aroma, shape, texture, and sensation in the mouth. Cats will willingly take medication if the formulation suits their preferences (Petry et al., 2014).

Cats are solitary hunters and obligate carnivores that tend to hunt smaller prey. They tend to tear flesh and organs such as the lungs, heart, kidneys, liver, and spleen from larger prey (Aldrich 2015). Cats have specific nutritional needs, particularly a protein requirement of 30% (Watson et al., 2023). Chicken liver is a high-protein nutrient source favored by carnivores. This hypothesis suggests that chicken liver could be a good drug filler for cats, meeting their palatability and nutritional needs. Silymarin, on the other hand, has long been used in traditional medicine and is known for its well-researched hepatoprotective benefits (Jaffar et al., 2024). The combination of chicken liver and silymarin is believed to help improve liver function and enhance animal palatability to the drug. This study aims to demonstrate the safety of chicken liver as a drug filler in paste form, supplemented with silymarin, through acute toxicity testing in mice.

MATERIALS AND METHODS

Research Preparation

This research was conducted over 10 months, from January to October 2024, at the UPHL Laboratory, School of Veterinary Medicine and Biomedicine (SKHB), IPB University. The chicken liver production process was carried out at PT Nutricell Pacific, and the formulation of chicken liver as a drug filler was carried out at the Pharmaceutical Laboratory, SKHB, IPB University.

Chicken Liver Paste Formulation

The chicken liver paste formulation was carried out based on the procedure in the study by Silva et al. (2020). The basic chicken liver paste formulation was made using the paste-forming ingredients xanthan gum, EDTA, and sufficient water. The basic paste formulation was combined with 10% liver extract and 0.2% silymarin as a treatment. The basic paste formulation was prepared by dispersing the paste-forming ingredients in distilled water containing other pre-dissolved excipients. The mixture was heated to 60°C and stirred continuously until a gel formed. Chicken liver flour was added using a mortar and pestle at a ratio of 10% (w/w).

pH MEASUREMENT, Organoleptic Testing, and Homogeneity Testing (Anggi 2016)

One gram sample of chicken liver paste was prepared, and the pH was measured using a pH meter on days 1, 3, 5, 7, 14, 21, and 28. The pH values were recorded, and the data were then processed. Organoleptic observations were conducted by pouring the sample into a container and observing the resulting color, odor, and taste. The color was compared to the desired specification, which was chocolate. Aroma was tested by smelling the preparation, with the desired aroma, which was organoleptically measured, liver odor.

The samples were observed and any changes recorded. Homogeneity of the preparation was assessed by measuring the mixing of the ingredients in the semisolid base. A 0.01 g sample of paste was taken from four different locations. Each sample was placed on a glass slide, and then, using another glass slide, its homogeneity was observed. Homogeneity was indicated by the orderly arrangement of the preparation on the slide.

Viscosity, Adhesion, and Spreadability Tests (Nayeem and Karvekar, 2011)

The paste was placed in a container and mounted on a viscometer. The viscosity of the paste was determined by observing the decipascal (dpas) value. The first test was conducted on the day the preparation was made, and repeated at intervals of days 3, 5, 7, 14, 21, and 28, along with the adhesion and spreadability tests.

The adhesion test involved taking 250 mg of paste and spreading it evenly on one slide, then covering it with another slide. The sample was then subjected to a 1 kg load for five minutes. The slides were then mounted on the adhesion tester, and the time was measured from the application of the load to the release of the slide.

The dissemination test involved placing 0.50 g of paste on a slide. The slide was then covered with another slide and left for one minute. The paste spread diameter will then be measured and the sample will be given an additional load every minute with a weight of 50 g to 1000 g, then the diameter will be measured again to see the effect of the load on the paste spread diameter.

Toxicity Testing Experimental Animals

The procedures for handling and using research animals have been approved by the Animal Ethics Commission, School of Veterinary Medicine and Biomedical Sciences (SKHB), IPB University, with approval number 185/KEH/SKE/III/2024. Twenty-five mice

were used. The mice were acclimatized for 14 days prior to the study to adapt to the environment and reduce stress levels. The mice were administered an anthelmintic (ivermectin) at a dose of 0.04 mg/kg body weight.

Toxicity Testing Experimental Design

The study was conducted using a Completely Randomized Design (CRD), with the lethal dose 50 (LD50) determination method referring to the BPOM (2022). A total of 25 female DDY mice were divided into five groups, with five mice per group. Group 1 was given liver paste without supplementation as a negative control. Treatment groups 2 through 5 were given liver paste at various dosages: 5, 10, 15, and 20 g/kg body weight. The liver paste was administered orally once on day 0 using a gastric tube.

Mice were monitored for toxicity and mortality for 14 days. Mice were weighed on days 0, 7, and 14. They were provided with food and water ad libitum throughout the study. The parameters monitored were mortality, weight gain, temperature, and clinical symptoms.

Blood Profile Test (Fleuryantari et al., 2018)

One mL of blood was drawn from mice using an EDTA tube on day 14. Blood profile examination was performed using a hematology analyzer (Vetscan HM5, PT. Mega Utama Medica, Indonesia). The hematology profile observed included red blood cells (RBCs), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, white blood cells (WBCs), lymphocytes, and granulocytes.

Data Analysis

The results were analyzed using variance analysis at a 95% confidence interval using SPSS 2.0 software. The analysis of variance was followed by Tukey's test. The research data were presented in tables and then analyzed descriptively.

RESULTS AND DISCUSSION

Stability of The Chicken Liver Paste Preparation

The results of the chicken liver paste test showed that it was in accordance with the expected results, with a brown color and a distinctive liver odor. The homogeneity test showed that the paste had an even texture and was free of coarse grains, indicating no significant changes after the manufacturing process. The pH test also showed appropriate results, at around pH 4.5. According to Thombre (2004), cats prefer acidic foods with a pH range of 4.5–5.5.

The results showed a significant difference in the chicken liver paste preparation compared to the paste base preparation (Table 1). This proves that chicken liver increases the viscosity of the paste preparation, making it easier to swallow. The adhesion test on both preparations yielded results that met the expected standard limits, which were above 4 seconds. The disseminatin test for the liver paste preparation provided greater spreadability compared to the paste base, thus facilitating easier spreading and absorption when applied. Overall, the stability test during the

Table 1. Results of organoleptic, pH, viscosity, and dissemination, adhesion tests on the chicken liver paste preparation

Sample	Basic Pasta	Liver Paste	Liver Paste + Silimaryn
Color	White	Brown	Brown
Taste	Tasteless	Chicken liver	Chicken liver
Smell	No Odour	Chicken liver	Chicken liver
Homogenity	Homogen	Homogen	Homogen
pH	7,10 ± 0,04 ^{b}	4,50 ± 0,08 ^{c}	4,50 ± 0,06 ^{c}
Viscosity (cP)	37.398,11 ± 726,76 ^{cd}	76.856,69 ± 12.057,18 ^{b}	76.814,67 ± 11.039,22 ^{b}
Dissemination test (mm)	43,09 ± 0,40 ^{bcd}	37,5 ± 2,16 ^{d}	37,5 ± 2,16 ^{d}
Adhesion test	More than 4 second	More than 4 second	More than 4 second

Note: Different superscripts in the same row indicate significantly different results ($p<0.05$).

observation process showed that the chicken liver paste met the requirements for cat consumption without complicating the swallowing process.

Acute Toxicity Test (LD50), Mortality and Body Weight of Mice After Administration of Silymarin-Supplemented Chicken Liver Paste

An acute toxicity test is used to observe side effects, particularly toxic effects caused by administering a substance to experimental animals over a short period (Sulastra et al., 2020). Mortality observations showed that no group of mice experienced mortality up to a dose of 20 g/kg BW (Table 2). Preparations that did not cause mortality or clinical abnormalities when administered at doses above 15 g/kg BW for 14 days were classified as relatively non-toxic (Klaasen and Watkins 2015).

According to Muhtadi et al. (2011), the apparent LD50 value is the highest dose that can technically be administered to test animals. Based on this statement, the apparent LD50 value for a single oral dose of silymarin-supplemented chicken liver paste for mice is greater than 20 g/kg body weight.

Statistical test results on body weight gain in mice (Table 2) indicate that administration of silymarin-supplemented chicken liver paste at doses of 5, 10, 15, and 20 g/kg body weight showed no significant difference ($p>0.05$) compared to the control group in terms of average body weight gain on days 0, 7, and 14 post-treatment. The fact that the preparation did not cause a 20% decrease in body weight in mice indicates that administration of the preparation did not cause any abnormalities or growth inhibition (Nurfaat 2016). This demonstrates that the chicken liver paste preparation does not inhibit growth and is relatively safe for consumption.

Clinical Symptoms of Mice After Administering Silymarin-Supplemented Chicken Liver Paste

Observations of the clinical symptoms presented in Table 3 show that all test animals (100% or 5 out of 5 mice) exhibited relatively calm behavior, clear red eyes, normal solid stool consistency, no tremors, no hypersalivation, or nerve paralysis. Furthermore, the test mice also had normal appetite and drinking habits, normal skin and coat condition, and normal breathing, reflexes, and urination. The absence of clinical symptoms in the mice in this study is a good result. Based on this, it can be concluded that the

Table 2. Mortality and body weight gain (BWG) of mice

	Silymarin-Supplemented Chicken Liver Paste (g/kg BW)				
Dosage	0	5	10	15	20
Mortality	0	0	0	0	0
BWG Week 1	2±1,1[a]	1,8±0,1[a]	1,7±0,5[a]	1,7±1,1[a]	2,2±0,8[a]
BWG Week 2	1,7±0,8[a]	2±0,9[a]	2±1,1[a]	2,2±0,8[a]	2,3±1,1[a]
Temperature (°C)	37±0.3[a]	36.6±0.7[a]	36.8±0,62[a]	36.9±0.4[a]	37±0.2[a]

Table 3. Observations of clinical symptoms (%) over 14 days in the group of mice given Silymarin-supplemented chicken liver paste

Clinical Sign	Group of Mice (g/kg BW)				
	0 (Control)	5	10	15	20
Nornal Behaviour on drink and appetite	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
Hair and Skin health	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
Breathing normally	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
Eye health	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
Stool consistency	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
Refleks	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
No Treamor	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
Urinating health	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
No Hypersalivation	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)
Incoordination	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)	100 (5/5)

administration of Silymarin-supplemented chicken liver paste in this study at a dose of up to 20 g/kg body weight is non-toxic and safe for consumption.

Body Temperature of Mice after Administration of Chicken Liver Paste Supplemented with Silymarin

Observations showed that the mice showed no temperature changes after administration of chicken liver paste supplemented with silymarin (Table 2). Changes in body temperature can indicate signs of toxicity. Drugs and other potentially toxic substances can affect the body temperature of living organisms. These changes in body temperature are generally indicated by hyperthermia (Mozafari et al., 2016). The mice's temperature ranged between 36.8-37.1°C. According to Ribeiro et al. (2022), the normal body temperature range for mice is 36.5-38.0°C. The temperatures exhibited by the experimental animals remained within this range. This indicates that administration of chicken liver paste supplemented with silymarin did not cause fluctuations in the mice's body temperature.

Hematology Analysis of Blood Samples after Administration of Chicken Liver Paste Supplemented with Silymarin

The hematology analysis of mice performed on day 14 showed no significant differences from the hematology results of mice. All parameters in the form of blood samples showed no significant differences from the standards determined by Haney et al. (2019). The hematology results can be seen in Table 4 below.

Red blood cell (RBC) counts showed no significant differences between treatment groups when compared to the negative control ($p>0.05$). The results also showed that the RBC count in all groups remained within the normal range. All groups had a normal RBC count range. The highest RBC count was found in the silymarin 4 group. This result indicates that silymarin does not interfere with erythropoiesis and may even have a mild stimulatory effect on red blood cell production. This finding is supported by research by Valenzuela et al. (1989), which showed that silymarin can increase ribosomal protein synthesis, which plays a crucial role in red blood cell formation.

Table 4. Hematology analysis of mice after administration of chicken liver paste supplemented with Silymarin

Hematology Parameter	Treatment group (g/kg BB)					
	Normal	0	5	10	15	20
RBC (10^6/µL)	6.36–9.42	7,57±0,55[a]	7,83±0,83[a]	8,47±0,67[a]	7,79±0,56[a]	8,59±0,80[a]
Hb (g/dL)	11–15.1	12,03±0,31[a]	12,76±0,50[a]	13,02±0,10[a]	12,45±0,86[a]	13,05±0,76[a]
Hct (%)	35–45.4	37,53±2,11[a]	38,76±2,29[a]	39,53±3,06[a]	37,53±1,98[a]	37,72±0,48[a]
MCV (fL)	45–60.3	50,54±2,82[a]	51,14±1,37[a]	53,50±1,82[a]	51,64±1,93[a]	52,19±1,79[a]
MCH (pg)	14.1–19.3	17,34±0,42[a]	17,95±1,62[a]	17,24±0,72[a]	17,84±0,51[a]	17,09±0,92[a]
MCHC (g/dL)	22.3–32	31,9±2,07[a]	31,83±0,28[a]	32,63±1,37[a]	32,77±0,92[a]	32,71±0,57[a]
RDW (%)	12.4–27	15,32±0,48[a]	15,25±0,36[a]	15,52±1,28[a]	15,22±1,38[a]	15,03±0,59[a]
PLT (10^3/µL)	592–2872	803±1,35[a]	1.030±0,29[a]	762±0,31[a]	817.6±1,81[a]	1.06±0,32[a]
MPV (fL)	5–20	4,81±1,30[a]	5,02±0,75[a]	4,78±0,63[a]	4,88±0,42[a]	4,30±0,35[a]
PDW (%)		17,02±0,22[a]	17,03±0,52[a]	17,12±0,28[a]	17,03±0,50[a]	16,76±0,25[a]
PCT (%)		0,27±0,12[a]	0,23±0,08[a]	0,28±0,02[a]	0,30±0,06[a]	0,25±0,03[a]
WBC (10^3/µL)	1.7–10.7	5,35±1,02[a]	4,91±0,84[a]	5,40±0,80[a]	5,40±1,20[a]	4,98±0,74[a]
Lymphocyte (10^3/µL)	0.9–9.3	4,23±0,34[a]	4,00±0,51[a]	4,43±0,52[a]	4,17±0,93[a]	3,93±0,51[a]
Monocyte (10^3/µL)	0–0.4	0,25±0,01[a]	0,22±0,05[a]	0,23±0,03[a]	0,14±0,08[a]	0,23±0,04[a]
Granulocyte (10^3/µL)	0.1–3	1,50±0,03[a]	1,50±1,40[a]	1,59±0,31[a]	1,52±0,36[a]	1,36±0,65[a]
Lymphocyte (%)	55.8–91.6	71,42±3,22[a]	73,00±5,83[a]	71,92±7,66[a]	72,67±13,03[a]	72,92±8,09[a]
Monocyte (%)	0–7.5	2,09±1,16[a]	2,04±1,67[a]	1,99±3,06[a]	2,15±3,14[a]	2,26±6,42[a]
Granulocyte (%)	6.6–45.8	43,30±2,16[a]	39,97±5,14[a]	44,30±5,21[a]	41,79±9,33[a]	39,25±5,10[a]

Hemoglobin (Hb) and hematocrit (Hct) levels in all treatment groups were within normal limits (p>0.05). This indicates that silymarin does not negatively impact hemoglobin synthesis or red blood cell volume. According to Pradeep et al. (2007), silymarin has antioxidant properties that can protect hemoglobin from oxidative damage, potentially helping maintain stable hemoglobin levels. Red blood cell indices, such as MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), and MCHC (Mean Corpuscular Hemoglobin Concentration), were also consistent and within normal limits across all groups, indicating that silymarin did not affect the morphology or hemoglobin composition of red blood cells. These results align with the study by Milić et al. (2013), which found that silymarin helps maintain red blood cell membrane integrity.

Red Cell Distribution Width (RDW) was slightly above the normal range (12.4-27%) in all groups (p>0.05). Although an increase in RDW can indicate variations in red blood cell size, its effect in this context appears to be minimal and does not indicate any signs of toxicity.

Platelet counts (PLT) in all treatment groups were within the normal range, indicating that silymarin does not negatively affect thrombopoiesis. Other platelet-related parameters such as Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), and Platelet-Crit (PCT) also showed no significant differences between groups. These results align with research by Chtourou et al. (2015), which reported that silymarin has no negative effects on platelet function and may even have a protective effect on excessive platelet aggregation.

White blood cell (WBC) counts in all groups were within the normal range. These results indicate that silymarin did not cause an excessive inflammatory response or suppress the immune system. A decrease in WBC counts due to drug usage can suppress the immune system and make the body susceptible to infection. According to research by Agarwal et al. (2006), silymarin has immunomodulatory effects that help maintain immune system balance without causing excessive activation. Differential analysis of white blood cells showed that the percentages of lymphocytes, monocytes, and granulocytes were within the normal range for all treatment groups. Although there was slight variation between groups, this difference was not statistically significant. These results indicate that silymarin did not cause significant changes in the distribution of immune cells.

CONCLUSION

Stability testing of the chicken liver paste revealed a homogeneous physical appearance, characteristic chicken liver odor, brownish color, pH, viscosity, adhesiveness, and dissemination. Acute toxicity testing of the silymarin-supplemented chicken liver paste showed no mortality during the 14-day observation period and no abnormal clinical symptoms. Body temperature, weight gain, and hematological profiles showed no significant differences. This demonstrates that the silymarin-supplemented chicken liver paste is a relatively non-toxic preparation.

AUTHORS CONTRIBUTION

P.T.P and L.N.S performed the experiments and data analysis for the chicken liver-based drug formulation. W.M designed and drafted the experimental model and the manuscript. A. and A.A.M. performed the experiments and data analysis for acute toxicity (LD50). The manuscript was read and approved by all author**s.**

"The authors declare that there is no conflict of interest with any party involved in this study."

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