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PHARMACOKINETIC PROFILE OF SNEDDS PREPARATION EXTRACT OF PUTRI MALU LEAVES

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A B S T R A C T

The Indonesian Ministry of Health reported that incidence of hepatitis in Indonesia has reached 20 million cases. As one of the preventive to reduce hepatitis disease, by consuming natural hepatoprotectors Putri malu plant. Therefore, Putri Malu needs to increase its bioavaibility in the body by making SNEDDS preparations. ***Purpose*** *of this research is to knowing the formulation of variations in the concentration of oil, surfactant and cosurfactant in the preparation of SNEDDS Putri malu leaf extract on pharmacokinetics including Cpmax, Tmax and T1/2 values.* ***Research method*** *is a laboratory experimental by varying the concentration of VCO: Tween 80: PEG 400, namely F1 (1:6:3), F2 (1:7:2) and F3 (1:8:1).* ***Results :*** *formulation of the SNEDSS of Putri malu leaves has nanoemulsion times at F1-F3 each 3.65, 14.78 and 25.61 seconds. The Cpmax value of the third formula gets a value of 500 ppm, Tmax the three formulas get the same Tmax value of 0 hours and for the T1/2 value at F1-F3 each 4.222, 6836, and 2.826 hours. The best formula is found F2, this can be seen at T1/2, the longer the drug can last in the body, the less frequency of taking the drug.*

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INTRODUCTION

The Indonesian Ministry of Health reported that incidence of hepatitis in Indonesia has reached 20 million cases. The Ministry of health recorded that the number of deaths due to hepatitis reached 51.100 every year. This hepatitis disease emerged when the COVID-19 pandemic had not yet overtaken the world. Hepatitis disease mostly attacks patients with an age range of 0-20 years and has fatal consequences on the function of the liver which acts as a metabolic organ (Kementerian Kesehatan RI, 2023)**.** Hepatitis is an inflammation of the liver caused by various infectious and non-communicable viruses that are the cause of various health problems, some of which can be fatal (Kementerian Kesehatan RI, 2023). As one of the preventive measures that can be done is by consuming hepatoprotectors.

Hepatoprotectors are compounds that can provide protection from liver damage, hepatoprotektors work through a mechanism to protect the liver from damage caused by drugs, toxins and other disorders (K et al., 2021). The use of chemical drugs in hepatitis patients is very risky because there are hepatoroxic substances in these drugs. One of the plants that is efficacious as a hepatoprotector is the Putri malu plant (Mimosa pudica Linn.) This plant grows wild and abundantly in Indonesia. In the Gorontalo area, this putri malu plant is often called mimosa. Based on the results of research from (Bagaskara et al., 2022)The leaf extract of the Putri malu plant (Mimosa pudica Linn.) showed hepatoprotective activity in white mice induced with ibuprofen which was characterized by a decrease in the levels of SGOT and SGPT produced by the liver of mice. Compounds that play a role in hepatoprotectors are flavonoids. One of the important factors so that the active substance can provide a maximum therapeutic effect and is acceptable for its use or use, namely by formulating it into pharmaceutical preparations. A pharmaceutical preparation that can increase the concentration of drug levels in the blood with nano-sized particles is to formulate the Putri malu leaf extract into the Self Nano-Emulsifying Drug Delivery System (SNEDDS). SNEDDS is a preparation with a nanoparticle formulation in the form of an isotropic mixture consisting of oil, surfactant, and co-surfactant which when it encounters gastro-intestinal fluid will spontaneously form nanoemulations (Michaelsen et al., 2019). According to (Tungadi, Thomas dan Gobel, 2021) the advantages of SNEDDS are that it can increase the bioavailability of the active drug substance, increase the dissolution rate and absorption of the active substance in the body. (Michaelsen *et al.*, 2019) stated that the SNEEDS formulation can increase pharmacokinetic values. Pharmacokinetics itself includes the value of Cpmax, Tmax and AUC0-∞. To determine the levels of Cpmax, Tmax and AUC0-∞, a test was carried out using the Crane Wilson method. Research related to preparation of SNEDDS for putri malu in testing the pharmacokinetic profile has never been carried out before.

Based on the description above, the formulation of the Putri malu leaf extract as a hepatoprotector in the SNEDDS preparation was carried out to increase the pharmacokinetic value ex vivo using the crane wilson method. This is done with the main hope of finding a solution to the mysterious acute hepatitis.

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RESEARCH METHOD

Tools and Material

Toolused in this study include: Sartorius® analytical balance, pyrex® glass beaker, blender, pyrex® measuring cup, erlenmeyer pyrex®, hot plate, watch glass, black cloth, stirring rod porcelain cup, horn spoon, spatula, magnetic stirrer, test tubes, Thermo Scientific®, Krisbow® ultrasonic cleaner, Toledo Multi Parameter®, UV Viss spectrophotometry, fume hood, crane & wilson, oven, glass jars and glass containers.

The materials used in this study included: Putri malu leaves (Mimosa pudisca Linn.), 70% ethanol, VCO, tween 80, PEG 400, citric acid, sodium citrate, phosphoric acid, sodium phosphate, hydrochloric acid, aquadest, ZnSO4, NaCl , Ba(OH)2, AlCl3, potassium acetate, dialysis membrane and filter paper.

Work Procedures

Making Simplicia and Putri Malu Leaf Powder

The leaves of the putri malu are cleaned of dirt or foreign plants that stick to the leaves by washing with water. Then drying using an oven with a temperature of 400C to dry and calculating the percentage of simplicia moisture content(Ibrahim, 2022; Utami et al., 2021).

Making Putri Malu Leaf Extract

1 kg of putri malu leaves extracted by maceration at room temperature for 5 x 24 hours using 10 liters of 70% ethanol. It is then thickened with a rotary evaporator (Utami et al., 2021).

SNEDDS Preparation

Table 1. SNEDDS Preparation Formula

Compound	Concentration			Utility
	F1	F2	F3	
Ethanol Extract of Putri malu leaves	500 ppm	500 ppm	500 ppm	Substance Active
VCO	1%	1%	1%	Oil Phase
Tween 80	6%	7%	8%	Surfactant
PEG 400	3%	2%	1%	Cosurfaktat

Mixing the oil phase (VCO) and active substance (Putri malu leaf extract), then adding surfactant (Tween 80), then adding cosurfactant (PEG 400) and stirring with a magnetic stirrer at 400 rpm (Ibrahim, 2022).

Nano Emulsified Time Test

Test emulsification time is carried out emulsified, a good emulsification time is less than 1 minute (Ibrahim, 2022).

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Crane & Wilson Pharmacokinetic Test

The method used iswithreverse small bowel pouch technique modified using a dialysis membrane. The experiment was carried out at 37oC. The mucosal compartment was filled with 500 ml of a pH 1.2 buffer solution (Systemic physiology). The dialysis membrane was filled with F1, F2, and F3 with SNEDSS. The dialysis membrane which already contains SNEDDS is inserted into the Crane and Wilson tubes which have been filled with systemic physiology solution. Sampling was carried out 8 times with an interval of 1, 2, 3, 4, 5, 6, 7, and 8 hours, the absorbance was read using UV-VIS spectrophotometry (Bardol *et al.*, 2023; Masloh *et al.*, 2023).

Flavonoid Spectrometry Test using UV-VIS

Determination of flavonoid levels begins with making a curverawquarcetin, then the sample at point E was read for absorbance by means of a 1 mL pipette then added 1 mL of 2% AlCl3 solution and 1 mL of 120 M potassium acetate using spectrometry with a wavelength of 510 nm (Sapiun *et al.*, 2020)**.**

RESULTS AND DISCUSSION

Water Content Putri Malu Leaves Simplicia

The parameter measured to determine the good quality of simplicia is water content. The average water content of simplicia contained in the Kemenkes RI, 2022 is <10.62%. The results of the water content test of Sesewanua leaf simplicia can be seen in Table 2.

Table 2.Percentage of Water Content in Putri Malu Leaves Simplicia

Simplicia	Gross Weight	Resulting Simplicia weight	% Water Content
Putri Malu Leaves	12.905 g	1.142 g	8,85%

Percentage of Ethanol Yield in Putri Malu

A good standard of extract yield based on the Kemenkes RI, 2022 ie not less than 7.2% and more than 10%. The percentage yield of the ethanol extract of the Putri malu leaves can be seen in table 3.

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Table 3. Percentage of Yield of ethanol extract of putri Malu Leaves

Extract	Simplicia weight	Produced Extract Weight	% Yield
Daun Putri Malu	500gram	41,6272 g	8,32 %

Nano Emulsified Time Test Results

Nano emulsified time is a description of the level of dissolution of a nano preparation in gastric fluid. The results of testing the emulsified time of the SNEDDS preparation are as shown in Table 4.

Table 4. Nano emulsified Preparation Time

Composition	Formula	Emulsdified time (second)
		Gastric Fluid
VCO:Tween 80: PEG 400	F1 (1:6:3)	13,65
	F2 (1:7:2)	14,78*
	F3 (1:8:1)	25,61*

*Significantly different from F1 <0,05

A good SNEDDS is SNEDDS which has an emulsified time. The standard of the emulsified time of a good SNEDDS preparation is less than 1 minute (Sapiun et al., 2024). The addition of tween 80 and PEG 400 can affect the emulsified time as quiet as SNEDDS. Variations in the concentration of PEG 400 decreased which had a faster emulsified time, while the variation in the concentration of tween 80 increased, which also increased the nano emulsified time produced.(Pade, 2022). The results in table 3. obtained that the three formulas had fast emulsification times. The best formula results with fast emulsification time are found in formula 1 (1:6:3) for gastric fluid for 13.65 seconds, when the emulsification time of a preparation is faster it will increase the absorption of the preparation. (Tungadi, Thomas dan Gobel, 2021; Sapiun *et al.*, 2023).

Wilson Crane Test Results and Pharmacokinetic Determination

Quarcetine Standard Standard Curve

The maximum wavelength obtained for quarcetin is 510 nm. At a wavelength of 510 nm, it is expected to provide maximum sensitivity to samples containing quarcetin (flavonoids). The absorbance measurement of the quarcetin standard curve can be seen in Figure 1.

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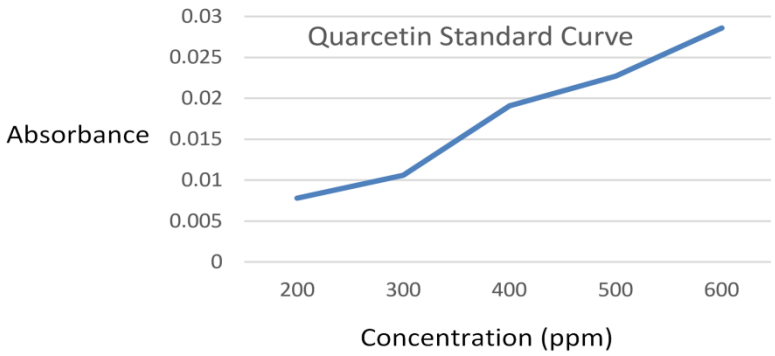

Figure 1. Quarcetine calibration curve at a maximum wavelength of 510 nm

The calibration curve is used to obtain a regression equation that will be used to calculate the flavonoid content in the test sample. The absorbance measurement of the standard quarcetin standard used UV-Vis spectrophotometry with a wavelength of 510 nm, and the regression value y=0.00339x+0.00405 with a correlation coefficient of r was close to 1. The results showed that the method used had good linearity requirements.

Bioavailability Test Results and Pharmacokinetic Determination

Determination of pharmacokinetic values was obtained by the concentration of flavonoid compounds present in the samples from the Crane Wilson test every hour. The concentration of flavonoid compounds contained in the test samples of each formula is shown in table 5.

Table 5. Results of Flavonoid Concentration

Time (Hour)	Concentration (ppm)		
	F1	F2	F3
1	498,452	498,097	497,834
2	498422	498,953	497,478
3	498,481	498,393	497,921
4	498,687	498,009	497,389
5	498,275	498,127	497,272
6	498,628	497,714	497,834
7	498,953	498,245	497,685
8	498,687	499,189	498,038

The results of the concentration of flavonoid compounds obtained from absorbance readings using UV-Vis Spectrophotometry using a wavelength of 510 nm. Then the concentration is used to calculate the value of Cpmax, Tmax and T1/2.

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Table 6. Bioavaibility Value

Sample	Cpmax Value (µg/mL)	T_0max Value (hours)	$T_{1/2}$ (hours)
F1	500	0	4,222
F2	500	0	6,836*
F3	500	0	2,826*

*Significantly different from F1 <0,05

Cpmax/peak plasma concentration obtained is 500 ppm. This means that the maximum drug concentration of SNEDDS F1, F2 and F3 that enters the systemic circulation after drug administration is 500 ppm which corresponds to the amount of active substance that can provide a therapeutic effect. The results obtained show that variations in the concentration of VCO : Tween 80 : PEG 400 in the F1-F3 formula provide good Cpmax results, this is in accordance with Priani, 2021 that SNEDDS preparation can optimal Cpmax values for the properties of medicina substances included in BCS class 2 and 3.

Tmax is the time when Cpmax is reached. SNEDDS preparations F1, F2 and F3 both provide a Tmax of 0 hours, which means that the active substance in the SNEDDS preparation can be absorbed immediately into the systemic circulation. The results obtained show that variations in the concentration of VCO : Tween 80 : PEG 400 in the F1-F3 formula provide very fast Tmax results. This is accordance with Zhang *et al.*, 2019 that SNEDDS preparations can provide a complex layer of phospholipids which accelerate the process of drug absorbtion across the gastro intestinal membrane.

T1/2 is the time when the plasma drug level decreases by half which will be related to the administration of the drug. F1 indicates a half-life of 4.222 hours which means it can be taken 6 times a day, F2 shows a half-life of 6.836 hours which means it can be taken 3 times a day and F3 shows a half-life of 2.826 hours which means it can be taken 8 times a day. A good half-life is found in formula 2, this is because the longer the drug can last in the body, the less the frequency of taking the drug. The frequency of taking medication often will reduce patient compliance in taking medication (Zhang *et al.*, 2019; Priani, 2021).

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

a. The formulation of the Self Nano-Emulsifying Drug Delivery System (SNEDSS) of Putri malu leaves which was divided into 3 formulas with varying concentrations of oil phase (VCO), surfactant (tween 80) and cosurfactant (PEG 400) had a nano-emulsion time at F1 (1:6: 3) which is 13.65 seconds, F2 (1:7:2) is 14.78 and F3 (1:8:1) is 25.61 seconds.
b. The pharmacokinetic values obtained for each formula are for Cp max the three formulas (F1, F2, F3) get the same Cpmax value, namely 500 ppm, for Tmax the three formulas get the same Tmax value, namely 0 hours and for the T1/2 value in F1 for 4.222 hours, F2 for 6.836 hours, and F3 for 2.826 hours. The best formula is found in F2, this can be seen at T1/2, the longer the drug can last in the body, the less the frequency of taking the drug.

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The frequency of taking medication often will reduce patient compliance in taking medication.

RECOMMENDATION

a. The formulation of Putri malu leaf extract in the form of Self Nano-Emulsifying Drug Delivery System (SNEDDS) can be used as a new innovation by the pharmaceutical industry as a new dosage product for the therapy and prevention of hepatitis.
b. *Self Nano-Emulsifying Drug Delivery System* (SNEDDS) Putri malu leaf extract can be used by the public as a more effective therapy and prevention option for hepatitis.
c. To increase the acceptability of the SNEDDS preparation, it is hoped that the Putri malu leaf extract can be developed in the form of SNEDDS soft shell capsules.

BIBLIOGRAPHY

Bagaskara, A., Triastuti, N., Yuliyanasari, N., Annisa Ayu Rezkitha, Y., Anas, M., & Indra Alfaray, R. (2022). Efficacy Of Putri Malu Leaf Plant (Mimosa Pudica Linn) As Hepatoprotectors On Ibuprofen Induced Hepatic Damage In White Mice (Mus Musculus). *Magna Medika: Berkala Ilmiah Kedokteran Dan Kesehatan*, *9*(1), 01.

Bardol, M. *Et Al.* (2023) "Pharmacokinetic Pharmacodynamic Modeling Of Analgesics And Sedatives In Children," *Paediatric Anaesthesia*, 33(10), Hal. 781–792. Tersedia Pada: Https://Doi.Org/10.1111/Pan.14712.

Ibrahim, W. (2022). *Formulasi Dan Karakterisasi Self Nano Emulsifying Drug Delivery System (SNEDDS) Fraksi Toluena:Etil Asetat Daun Sesewanua (Clerodendrum Fragrans Wild.)*. Poltekkes Kemenkes Gorontalo.

K, A. P. G., Wati, A., Farmasi, S., Kesehatan, F. I., Kesehatan, I., & Medika, G. (2021). Penentuan Minimum Dosis Terapi Dan Minimum Toksik Ekstrak Etanol Buah Sawo Manila (Manilkara Zapota (L .) P . Royen) Sebagi Hepat. *Jurnal Inovasi Kesehatan*, *3*(1).

Kemenkes RI (2022) *Suplemen I Farmakope Herbal Indonesia*. II. Diedit Oleh K.K. RI. Jakarta: Kementerian Kesehatan RI.

Kementerian Kesehatan RI (2023) "Hepatitis 'Menjaga Hati Untuk Kehidupan,'" *Mediakom*, Hal. 30.

Masloh, S. *Et Al.* (2023) "Challenges And Opportunities In The Oral Delivery Of Recombinant Biologics," *Pharmaceutics*, 15(5).

Michaelsen, M.H. *Et Al.* (2019) "Fenofibrate Oral Absorption From SNEDDS And Super-SNEDDS Is Not Significantly Affected By Lipase Inhibition In Rats," *European Journal Of Pharmaceutics And Biopharmaceutics*, 142(January), Hal. 258–264.

Multazam, S., Cholissodin, I., & Adinugroho, S. (2020). Implementasi Metode Extreme Learning Machine Pada Klasifikasi Jenis Penyakit Hepatitis Berdasarkan Faktor Gejala. *Jurnal Pengembangan Teknologi Informasi Dan Ilmu Komputer*, *4*(3), 789–797.

Pade, D. F. M. (2022). *Formulasi Dan Karakterisasi Self Nano- Emulsifiying Drug Delivery System (SNEDDS) Fraksi N-Heksan:Etil Asetat Daun Sesewanua (Clerodendrum Fragrans Wild.)*. Poltekkes Kemenkes Gorontalo.

http://doi.org/10.22216/jk.v5i2.5717
Published by LLDIKTI Wilayah X

Jurnal Katalisator Vol 9 No. 1 (2024) 163-171

Priani, S.E. (2021) "Kajian Pengembangan Sediaan Self Nanoemulsifying Drug Delivery System (SNEDDS) untuk Penghantaran Agen Antidiabetik Oral," *Jurnal Mandala Pharmacon Indonesia*, 7(2), hal. 171–187.

Sapiun, Z. *Et Al.* (2020) "Determination Of Total Flavonoid Levels Of Ethanol Extract Sesewanua Leaf (Clerodendrum Fragrans Wild) With Maceration Method Using UV-Vis Spectrofotometry," *Pharmacognosy Journal*, 12(2), Hal. 356–360.

Sapiun, Z. *Et Al.* (2023) "Formulation And Characterization Of Self Nano-Emulsifying Drug Delivery System (Snedds) Fraction Of N-Hexane: Ethyl Acetate From Sesewanua Leaf (Clerodendrum Fragrans Wild.)," *International Journal Of Applied Pharmaceutics*, 15(2), Hal. 72–77.

Sapiun, Z. *Et Al.* (2024) "Modifying Fraction Extracted From Sesewanua (Clerodendrum Fragrans Wild) Leaves In Snedds Preparations: Characterization And Bioavailability Test," *International Journal Of Applied Pharmaceutics*, 16(2), Hal. 255–263. Tersedia Pada: Https://Doi.Org/10.22159/Ijap.2024v16i2.49372.

Tungadi, R., Thomas, N.A. Dan Gobel, W.G. Van (2021) "Formulasi, Karakterisasi, Dan Evaluasi Drops Liquid Self Nano-Emulsifying Drug Delivery System (SNEDDS) Astaxanthin," *Indonesian Journal Of Pharmaceutical Education*, 1(3), Hal. 168–178.

Utami, M. P., Kholis, A., Mulyasari, I., Noor, N., & Fadel, M. N. (2021). Aktivitas Antibakteri Krim Ekstrak Daun Putri Malu (Mimosa Pudica L.) Terhadap Bakteri Propionibacterium Acnes Penyebab Jerawat. *Prosiding 14th Urecol: Seri Kesehatan*, 242–252.

Zhang, J. *et al.* (2019) "Mechanistic studies on the absorption enhancement of a self-nanoemulsifying drug delivery system loaded with norisoboldine-phospholipid complex," *International Journal of Nanomedicine*, 14, hal. 7095–7106.

http://doi.org/10.22216/jk.v5i2.5717
Published by LLDIKTI Wilayah X