

CHAPTER I INTRODUCTION

1.1 Background

Diabetic mellitus (DM) is a metabolic disease with chronic hyperglycemia caused by abnormalities in insulin secretion, insulin deficiency or both.¹ DM is the cause of increasing mortality rates in the world. The International Diabetic Federation (IDF) in 2021 that Indonesia is ranked 5th in the country with the most DM sufferers and in 2045 it is estimated that there will be an increase from 19.5 million to 28.6 million sufferers.² DM causes various complications, one of which is foot wounds. In Indonesia, 15% of sufferers experience wounds due to diabetic, with an amputation rate reaching 30% and a mortality rate of 32%.³

DM sufferers with foot infections will develop *intogangrene* and risk causing amputation cases. As many as 14.3% of post-amputation patients died within a year and 37% died 3 years later.⁴ Diabetic wound conditions mostly experience edema of less than 2 cm, pink and inflammatory. DM patients with infection criteria marked by fever, redness and edema in the feet need to be hospitalized for intensive treatment.⁵

The use of herbal medicine is widely chosen because of its fewer side effects and affordability, one of the potential plants is kersen. Kersen leaves contain flavonoids, saponins, polyphenols and tannins. Flavonoids in kersen leaves have the potential as antioxidants, hepatoprotectors, antibacterials, analgesics, anti-inflammatory, anti-cancer and antiplatelet.⁶ At concentrations of 3% and 5%, the ethanol extract of kersen leaves had anti-inflammatory effects on mice.⁷

¹ PERKENI, *Pedoman Dan Pencegahan Diabetes Mellitus Tipe 2 Di Indonesia*, ed. Soebagijo Adi Soelistijo, 1st ed. (Jakarta, Indonesia: PERKENI, 2021).7–9

² International Diabetes Federation, *IDF Diabetes Atlas IDF Diabetes Atlas*, ed. Edward J Boyko *et al.* (Berkeley, 2021), www.diabetesatlas.org.

³ PERKENI, *Pedoman Dan Pencegahan Diabetes Mellitus Tipe 2 Di Indonesia*.3–4

⁴ Diya Rashida Binti Abu Rahman and Tharshani Devi Srinivasagam, *Diabetes Mellitus Tipe II Dan Diabetic Foot*, Universitas Udayana, 2018.

⁵ Eka Fitria *et al.*, “Karakteristik Ulkus Diabetikum Pada Penderita Diabetes Mellitus Di RSUD Dr. Zainal Abidin Dan RSUD Meuraxa Banda Aceh,” *Buletin Penelitian Kesehatan* 45, no. 3 (2017): 153–160.

⁶ Anita Dwi Puspitasari and Lean Syam Prayogo, “The Effect of Boiling Time on Total Flavonoid Content of Kersen Leaves (*Muntingia calabura*),” *Chemical Engineering Innovation* 1, no. 2 (2016).

⁷ Safriani Rahman, Aulia Wati, and Eka Mega Asariningtyas, “Anti-inflammatory Effect of Ethanol Extract of Kersen Leaves (*Muntingia calabura L.*) on Mice (*Mus musculus*),” *As-Syifaa Scientific Journal* 9, no. 1 (2017): 51–57, <https://doi.org/10.33096/jifa.v9i1.244>.

Meanwhile, at a concentration of 40%, kersen leaf extract effectively inhibits *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria.⁸

Plants with their various benefits are in line with the word of Allah SWT in the Qur'an, Surah Yaseen, verse 33, namely:

وَأَيُّهُمُ الْأَرْضُ الْمَيِّتَةُ أَحْيَيْنَاهَا وَأَخْرَجْنَا مِنْهَا حَبًّا فَمِنْهُ يَأْكُلُونَ

Meaning: “And a sign for them is the dead earth; We give it life and bring forth from it grain, and from it they eat.”⁹ This verse explains the power of Allah, including reviving the barren earth to life with green plants and grains which are the main components of life and staple food.¹⁰ The words “from it they eat” mean that the plants and seeds produce edible fruit. So it is seen that enjoyment is the result of the living earth to be used.¹¹ The form of plant utilisation is as a medicinal ingredient.

Treatment of infections Diabetic wounds is usually treated empirically using antibiotics with accurate bacterial identification to improve the therapeutic approach and prevent bacterial resistance. *Staphylococcus aureus* (*S. Aureus*) is the most common bacteria found in diabetic infections.¹² This condition makes the wound more difficult to treat. To reduce the risk of bacterial resistance, it is necessary to minimize the use of antibiotics.¹³ Efforts to optimize the treatment of diabetic wounds can be formulated in nanoparticle preparations.

The use of nanoparticles in pharmaceutical preparations with an emulsification system measuring less than 100 nm can change the texture, transparency and form of the preparation to be like water and increase penetration

⁸ Gabriella Alouw, Fatimawali Fatimawali, and Julianri Sari Lebang, “Antibacterial Activity Test of Ethanol Extract of Kersen Leaves (*Muntingia calabura* L.) Against *S. aureus* and *Pseudomonas aeruginosa* Bacteria Using Well Diffusion Method,” *Jurnal Farmasi Medica/Pharmacy Medical Journal (PMJ)* 5, no. 1 (2022): 36, <https://doi.org/10.35799/pmj.v5i1.41430>.

⁹ *The Holy Quran*, Yaseen [36]:33.

¹⁰ Wahbah Az-Zuhaili Translated by Abdul Hayyie Al-Kattani *et al.*, *Tafsir Al-Munir* Volume 12, 8th ed. (Depok: Gema Insani, 2016)., 31 – 43

¹¹ Hamka, *Tafsir Al-Azhar: Jilid 7*, 1st ed. (Depok: Gema Insani, 2015)., 417 – 419.

¹² Priti Shah *et al.*, “Wagner ’ s Classification as a Tool for Treating Diabetic Foot Ulcers : Our Observations at a Suburban Teaching Hospital,” *Cureus* 14, no. 1 (2022): 1–11.

¹³ Shofiuddin Al Mufid *et al.*, “Nano-Oxy : Diabetic Ulcer Treatment Using Oxygen Nanoparticles Concept as Innovation in Reducing Amputation Rates and Antibiotics Usage,” *World Journal of Advanced Research and Reviews* 13, no. 01 (2022): 1.

into the skin.¹⁴ Nano preparations have a smaller particle size distribution than traditional spray preparations and a larger surface area which can increase drug solubility, improve bioavailability and stability, control drug release and optimize absorption.¹⁵ Previous research has shown that 40% sea cucumber extract nanospray is more effective as a diabetic wound healer than penicillin.¹⁶ Therefore, this research needs to be carried out to alleviate the condition of diabetic wounds which are complicated to treat by utilizing natural ingredients as innovative preparations nanospray which has various advantages.

1.2 Formulation of the problem

1. How characteristics of the preparation-nanospray kersen leaf extract?
2. How effective is it nanospray of kersen leaf extract on diabetic wounds in experimental animals?

1.3 Research purposes

1. Know the characteristics of the preparation nanospray kersen leaf extract.
2. Knowing the effectiveness nanospray of kersen leaf extract on diabetic wounds in experimental animals.

1.4 Benefits of research

1. Theoretical Benefits

The theoretical benefits of this study are to be additional learning literature and broaden insight into the formulation of nanospray preparations and their effectiveness for treating diabetic wounds.

2. Practical Benefits.

Helps relieve diabetic wounds, increases the economic value of kersen leaves and finds innovations in halal diabetic wound treatment that have the potential to be produced commercially.

¹⁴ Makio Naito et al., *Nanoparticle Technology Handbook*, 3rd ed. (Amsterdam, Netherlands: Elsevier B.V., 2018)., 426 – 428

¹⁵ Rui Chen *et al.*, “Formulation and Characterization of Voriconazole Nanospray Dry Powder,” *Pharmaceutical Development and Technology* 7450 (2020): 9–13.

¹⁶ Nada Hanifah *et al.*, “Nanospray TRISWHEAT (Teripang Super Wound Healing Agent) From Teripang Extract As Healer of Diabetes Mellitus Wounds Infected by MRSA (Methicillin Resistant *S. aureus*) Bacteria,” *Journal of Veterinary Science* 36, no. 1 (2018): 40–45.

1.5 Authenticity of Research

Research on nano formulation and antibacterial effectiveness of kersen leaves has been conducted by several researchers as shown in table 1 below.

Table 1 Authenticity of Research

Research Title	Research methods	Variable	Results	Research Differences
Development of Nanoparticles of Kersen Leaf Extract (Muntingia calabura L) Using Self Nano Emulsifying Drug Delivery System (SNEDDS) Technique for Antibacterial Applications ¹⁷	Experimental	Dependents: Evaluation of the character of nanospray preparations of kersen leaf extract and the antibacterial effectiveness of <i>S. Aureus</i> Independent: SNEEDS technique of leaf extract	SNEDDS of kersen leaf extract with oil, surfactant and cosurfactant formulation with a ratio of 6:1:1, namely 6 parts of tween 80, 1 part of PEG 400 and 1 part of VCO. The particle size test of SNEDDS kersen leaf extract was 12.4 nm, zeta potential 30.8 mv, drug loading concentration 2%/5ml, emulsification time 49.55 seconds and stable for 4 hours. SNEDDS kersen leaf extract has better antibacterial power against <i>S. Aureus</i> than kersen leaf extract.	Dependents: Evaluation of the characteristics of nanospray preparations and wound healing in mice infected with <i>S. Aureus</i> Independent: The concentration of kersen leaf extract
Nanospray TRISWHEAT (Sea cucumber Super Wound Healing Agent) from Sea cucumber Extract as a Healer for Diabetic Mellitus Wounds Infected with MRSA (Methicillin Resistant <i>S. Aureus</i>) Bacteria ¹⁸	Experimental	Dependents : Healing of wounds in diabetic mice infected with MRSA bacteria Independent : Sea cucumber extract nanospray	Nanospray of 40% sea cucumber extract is more effective as a wound healer for diabetic mice infected with MRSA than penicillin.	Dependents : Effect of wound healing on mice infected with <i>S. Aureus</i> Independent : nanospray kersen leaf extract

¹⁷ Septiana Indratmoko, Asep Nurrahman Yulianto, and Axl Aprizal Herawan, "Development of Nanoparticles of Kersen Leaf Extract (Muntingia calabura.l) Using Self Nano Emulsifying Drug Delivery System (SNEDDS) Technique for Antibacterial Applications," Jurnal Pharmaqueous STIKES Al-Irsyad Al-Islamiyyah Cilacap 2, no. 1 (2020): 27–35, <http://e-jurnal.stikesalirsyadclp.ac.id/index.php/jp>.

¹⁸ Hanifah *et al.*, "Nanospray TRISWHEAT (Teripang Super Wound Healing Agent) From Teripang Extract As A Healer Of Diabetic Melitus Wounds Infected By MRSA (Methicillin Resistant Staphylococcus Aureus) Bacteria.", Op. cit.

The novelty compared to the research of Indratmoko *et al.* 2020 is in the dependent variable of evaluating the character of the kersen leaf extract preparation and the antibacterial effectiveness test for *S. Aureus*. while in this study the evaluation of the characteristics of nanospray preparations and wound healing of mice infected with *S. Aureus* and in the independent variable of the study by Indratmoko *et al.* 2020, the difference in SNEEDS concentration in oil, surfactants and cosurfactants, while in this study the difference in concentration in kersen leaf extract.

The difference with the research of Hanifah *et al.* 2018 on the dependent variable, namely the healing of wounds of diabetic rats infected with MRSA bacteria and histopathological data and the independent variable of nanospray of sea cucumber extract. While in this study the effect of healing wounds of rats infected with *S. Aureus* and the independent variable of nanospray of kersen leaf extract. Based on the literature study, the authenticity of this study can be stated.