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Nano Suspension of Soursop Leaf Extract as A Candidate for Future Diabetes Drugs

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Abstract

Diabetes mellitus remains a global health challenge despite advances in pharmaceuticals. Current antidiabetic drugs, though effective, have limitations such as side effects, high costs, and variable patient responses. This has fueled research into alternative therapies, especially from medicinal plants. Soursop leaves (Annona muricata L.) show promising antidiabetic effects in vitro and in vivo but suffer from poor bioavailability typical of plant compounds. Nanotechnology offers a promising way to improve drug delivery and efficacy. This study evaluated the antidiabetic potential of soursop leaf extract formulated as nanoparticles (Nano Suspension of Soursop Leaf Extract as a Candidate for Future Diabetes Drugs NEDS) versus conventional extract (EDS) in streptozotocin-induced diabetic rats (n=35, 7 groups). Diabetes was induced via streptozotocin and nicotinamide injections. Treatment groups received NEDS or EDS at 100, 200, or 300 mg/kg doses; controls included glibenclamide and untreated groups. Blood glucose was measured at baseline, day 7, and day 14, analyzed by ANOVA ($p<0.05$). Results showed that the nanoparticle formulation enhanced glucose-lowering effects significantly. NEDS at 300 mg/kg matched the efficacy of glibenclamide by day 14. The findings indicate that chitosan-based nanoencapsulation boosts the antidiabetic activity of Annona muricata leaf extract, suggesting a promising avenue for new diabetes treatments. Further mechanistic, pharmacokinetic, and safety studies are needed to confirm clinical potential.

Keywords: *Antidiabetic; Diabetic; Soursop; Nanoparticle*.

INTRODUCTION

One of the causes of human death is various disease conditions; diseases are known to have undergone a long evolution as human evolution progresses (Harari, 2014). One of the diseases that emerged after the long evolution of humans is a disease that causes disturbances in human blood sugar levels, commonly known as "diabetes." Diabetes is a disease that causes human blood sugar levels when in post-prandial conditions to have level above average numbers (120 mg/dL > Normal < 140 mg/dL); this is briefly caused by disorders that occur in the pancreas organ in secreting insulin, insulin is known to be associated with the management of glucose into an energy source in human organs (Tamilselvi & Kokilavani, 2013; Panari & Vegunarani, 2016; Vijay & Kumbhakar, 2016). Since it first appeared, diabetes is still a problem that has not been wholly resolved until now. Diabetes is known as a disease with a high mortality rate; this makes diabetes not only an individual problem but also a global concern (Chen et al., 2023).

The global burden of diabetes has reached epidemic proportions, with the International Diabetes Federation (2021) reporting approximately 537 million adults living with diabetes worldwide, a figure projected to rise to 783 million by 2045. Type 2 diabetes mellitus (T2DM)

accounts for approximately 90-95% of all diabetes cases, characterized by progressive insulin resistance and pancreatic β-cell dysfunction. The pathophysiological complexity of diabetes extends beyond glycemic dysregulation to encompass cardiovascular complications, nephropathy, retinopathy, and neuropathy, collectively contributing to significant morbidity and mortality. Despite advances in pharmacotherapy, the quest for optimal diabetes management remains incomplete due to treatment gaps, medication non-adherence, and socioeconomic barriers to healthcare access, particularly in low- and middle-income countries (Maslikah et al., 2025).

Like other problems humans face, humans try to solve the problem of diabetes with all available resources. Science, which is a biological child of the philosophy of positivism (Russell, 2004), is one of the human resources that continue to be developed to solve the problem of diabetes. The remarkable development of science, from the golden age of Islam (Masood, 2017) to the age of modern science today, shows the extraordinary efforts that man can achieve. Various basic sciences such as mathematics, biology, chemistry, and physics have been developed to solve the problem of diabetes. Various diabetes drugs have been discovered, of which the most common are drugs taken orally; various mechanisms of action ranging from DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 agonists, and various other mechanisms of action have resulted in the remarkable development of diabetes treatment (Arun et al., 2022; Wijayanti et al., 2020; Varma & Dighe, 2022; Deshpande et al., 2013; Dowarah & Singh, 2020). However, these remarkable developments have not been able to solve the problem of diabetes completely; various factors, including side effects and the ability of drugs that are less effective in some cases, make current drugs seem to be defeated by this disease (Stein et al., 2013; Hossain & Pervin, 2018; Melander, 1996; Singh, 2016; Briones et al., 2016; Kadrić et al., 2021).

Contemporary oral antidiabetic agents, while mechanistically diverse, present several therapeutic limitations that necessitate continued drug development efforts. Metformin, the first-line agent for T2DM, is associated with gastrointestinal disturbances and rare but serious lactic acidosis. Sulfonylureas carry risks of hypoglycemia and weight gain. Thiazolidinediones, though effective insulin sensitizers, are linked to fluid retention, bone fractures, and cardiovascular concerns. Newer agents such as DPP-4 inhibitors and SGLT2 inhibitors, despite improved safety profiles, present cost barriers and are not universally effective across patient populations. Furthermore, long-term glycemic control often deteriorates due to progressive β-cell failure, necessitating combination therapy or insulin initiation. These limitations underscore the urgent need for alternative therapeutic strategies with enhanced efficacy, improved safety profiles, and greater accessibility—criteria potentially fulfilled by plant-derived pharmaceuticals enhanced through nanotechnology.

The problem of diabetes that has not been resolved makes humans continue to develop science to create various advanced technologies to help solve this problem. Humans continued to learn and improve their self-knowledge (Harari, 2016; Harari, 2018) and nanoparticles were discovered (Jeevanandam et al., 2018). Nanoparticles are the most impactful breakthrough in the history of human discovery. Nanoparticles are like King David or known as the Prophet David in Islamic terminology, while it is one of the analogies that are very suitable because little David was able to defeat Goliath (Islamic Terminology: Jalut) who had a large body so quickly (Gladwell, 2013; Isser, 2003). It is not an exaggeration to say that nanoparticles are

small objects that have a significant impact, considering that the impact, especially in the world of health, is vast and very helpful for the development of science in the medical field to date (Wolfram et al., 2015; Mauricio et al., 2018; Murthy, 2007; Joseph et al., 2023; Markowska et al., 2013; Youssef et al., 2019). Nanoparticles are also known to have succeeded in increasing the potential ability of biological activity of various plants with potential as drugs (Alam et al., 2021; El-Borady et al., 2023; Rajan et al., 2015; Logeswari et al., 2015; Bankar et al., 2010; Khalil et al., 2012; Vivek et al., 2011; Küünal et al., 2018; Ahmed et al., 2016; Ghosh et al., 2015; Bayrami et al., 2020; Sher et al., 2023; Rudayni et al., 2023; Khan et al., 2023).

Science about the ability of nanoparticles to increase the potential biological activity of plants, especially in the treatment of diabetes, is very beneficial, considering that plants are one of the sources that can be found to develop antidiabetic drugs most easily and cheaply. Plants have also earned scientists the highest scientific prize, the Nobel Prize (Su & Miller, 2015; Efferth et al., 2015; Molyneux & Ward, 2015; Dlugónska, 2015; Benelli, 2018; Kende, 1998; Owens, 2015). Of the various medicinal plant parts developed to search for potential new antidiabetic drugs, soursop leaf (Annona muricata) is one of the most researched and has shown outstanding results (Martin del Campo-Rayas et al., 2022; Atanu et al., 2021; Berawi et al., 2017; Chowdhury et al., 2021; Ratya, 2014; Sovia et al., 2016; Malviya et al., 2010; Subaraman et al., 2020). Various analyses conducted show that Annona muricata contains several secondary metabolites that promise a wide range of pharmacological activities for humans (Kelechi et al., 2016; Okoro et al., 2016; Mohammed et al., 2021).

This research focuses on developing nanoparticle preparations using soursop leaves (Annona muricata) to see their potential as an antidiabetic. Specifically, this study addresses a critical research gap by investigating whether chitosan-based nanoencapsulation of soursop leaf extract enhances its antidiabetic efficacy in a streptozotocin-induced diabetic rat model. The novelty of this investigation lies in the direct comparative evaluation of conventional extract versus nano-formulated extract across multiple dosage levels, providing dose-response insights essential for therapeutic optimization. Furthermore, this study contributes to the growing body of evidence supporting nanotechnology-enhanced phytomedicine as a viable, cost-effective, and accessible approach to diabetes management, particularly relevant for resource-limited settings where herbal medicines are culturally accepted and economically feasible. The urgency of this research is underscored by the escalating global diabetes prevalence, the limitations of current pharmacotherapy, and the pressing need for innovative therapeutic modalities that combine efficacy, safety, and affordability. By bridging traditional ethnomedicine with cutting-edge nanotechnology, this investigation exemplifies translational research aimed at addressing unmet clinical needs in diabetes care.

RESEARCH METHOD

This study used soursop leaves originating from Pangandaran, West Java. In addition, this study also used 70% alcohol (sigma aldrich), aquadest (Brataco), beakers (Pyrex), chitosan (Planet Kimia), DMSO (Merck), magnetic stirrers (DAIHAN Scientific Indonesia), oral sonde for experimental animals, pH meter, streptozotosin (sigma aldrich), Sodium Tri Poly Phosphate (NaTPP), and UV-Vis Spectrometers (Shimadzu 1800).

The experimental animals involved in this study were white rats (Sprague dawley) that met the established inclusion criteria. The animals are male, 8 weeks old, weigh 120 grams,

are in good health, and do not suffer from diabetes mellitus with random blood glucose levels below 10.4 mmol / L or 187.2 mg / dL. The number of experimental animals used in this study was calculated using the Federer formula. Replication was carried out to avoid the possibility of experimental animals dying (f) = 25% during the study; then the replication magnitude was multiplied by 1/1 – f, so: 1/(1-0.25) x 5 = 6.67 = 7 (sample size rounded). The number of samples in this study was seven individuals per treatment group, so the overall sample size was 35 heads. Before the study began, mice were acclimatized for five days in an environment with a light/dark cycle of 12 hours and 12 hours of darkness, with temperatures between 29-31°C [62-65]. Rats were given free access to commercial rat feed and drinking water during the entire study period. The research has received ethical approval from the animal ethics commission iRATco VLS with letter number B-361/V/DI.05.07/1/2022.

To induce diabetes mellitus in rats, they were given a single intraperitoneal injection with streptozotocin as much as 30 mg/kg body weight. Streptozotocin is dissolved in a cold citrate buffer solution with a concentration of 0.1 M and has a pH of 4-5. Nicotinamide administration was also intraperitoneally at 100 mg/kg body weight in rats satisfied overnight. Induction of diabetes was evaluated by measuring glucose levels in the tail vein blood using a glucometer after 72 hours (Seetharaman et al., 2023; Bamisaye et al., 2023; Gupta et al., 2023; Manjunatha, 2023; Govindan et al., 2023).

Antidiabetic therapy was carried out after experimental animals were confirmed to have diabetes; each mouse that received the intervention was given soursop leaf extract in the form of nanoparticles with a concentration in mg/kg body weight, 100, 200, and 300. While with concentrations in mg/kg body weight, the extract group was given 100, 200, and 300 doses. The positive control group used glibenclamide with a 5 mg/kg body weight concentration, while the negative control group did not receive any intervention (Figure 1).

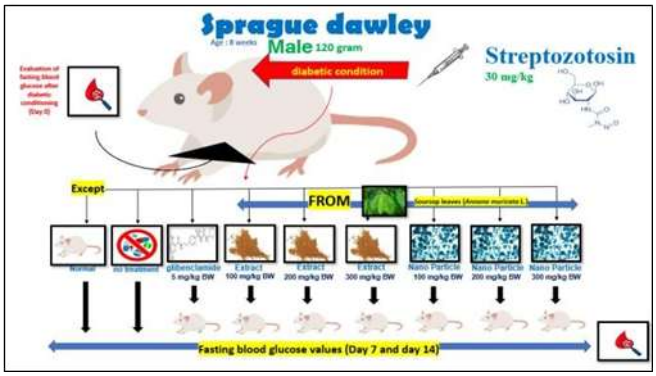

Figure 1. Research Model

RESULTS AND DISCUSSION

On day 0 (Figure 2), it was observed that the control group showed an average blood glucose level of 106.90. Theexperimental group designated as negative controls showed an average of the highest blood glucose levels, 260.91. Meanwhile, another experimental group, including positive controls, consisting of EDS 100, EDS 200, EDS 300 (EDS = Soursop leaf extract), NEDS 100, NEDS 200, and NEDS 300 (NEDS = nanoparticle Soursop leaf extract), showed elevated blood glucose levels above normal glucose conditions compared to the standard group. ANOVA analysis revealed statistically significant differences among the groups on day 0, with p-level less than 0.05.

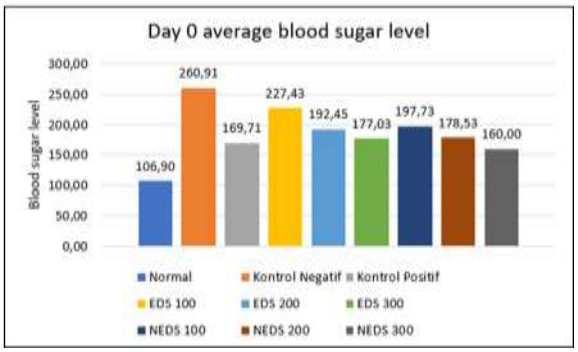

Figure 2. Day 0 - average blood sugar level

On the seventh day (Figure 3), the average blood glucose level of the regular group increased to 108.46. However,the rise in blood sugar of the regular group is descriptively not significant, and this may be influenced by food. The group assigned as negative controls showed an average of the highest blood glucose levels of 283.89. Other experimental groups, namely EDS 100, EDS 200, EDS 300, NEDS 100, NEDS 200, and NEDS 300, showed a decrease in blood glucose levels, as observed in the positive control group. ANOVA analysis showed significantdifferences among the groups on day seven, with p-level less than 0.05.

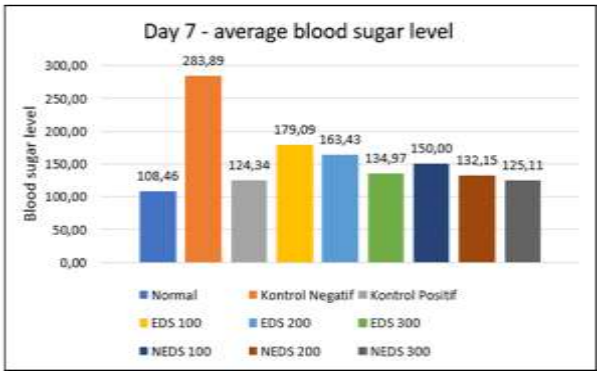

Figure 3. Day 7 - average blood sugar level

On the fourteenth day (Figure 4), the usual group showed an average blood glucose level of 108.80. The group assigned as negative controls showed an average high blood glucose level of 312.57. The positive control group showed a significant reduction in blood glucose levels, while the experimental group consisting of EDS 100, EDS200, EDS 300, NEDS 100, NEDS 200, and NEDS 300 showed the same. The results of the ANOVA analysis showed a statistically significant difference among the groups on day 14, with a p-value of less than 0.05. The NEDS 300 group showed descriptively insignificant differences from the positive control group, suggesting thatNEDS 300 is thought to have the same capabilities as the positive control group.

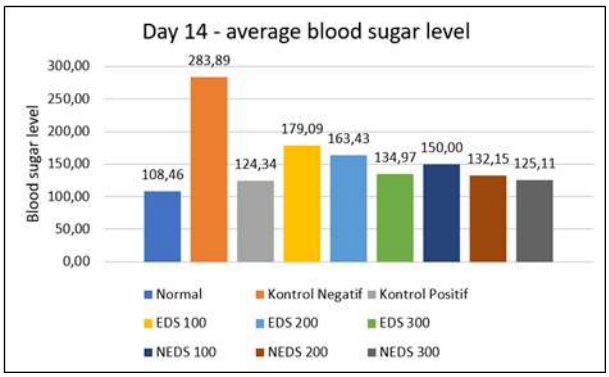

Figure 4. Day 14 - average blood sugar level

Based on the results of observations for 14 days (Figure 5), the NEDS group has better effects when compared tothe EDS group in terms of lowering the blood sugar levels of fasting rats modeled with diabetic conditions.

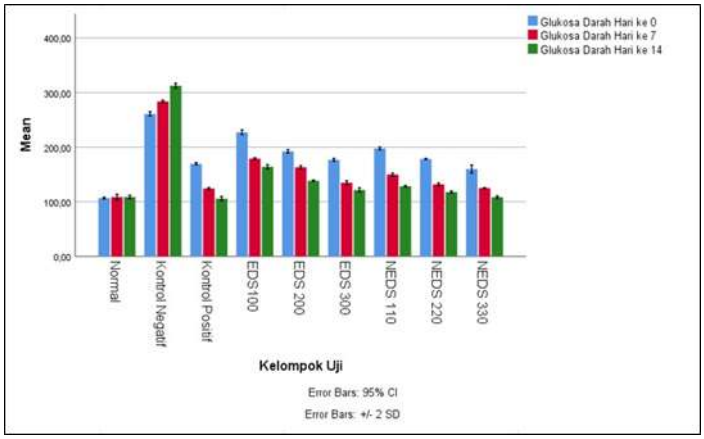

Figure 5. Average level of blood sugar after 14 days

DISCUSSION

Understanding and tracking the modulation of blood glucose in diabetic rats requires analysis of fasting blood glucose levels in a model system. Similar blood glucose dysregulation is frequently observed in diabetic rats as it is in diabetic people. Compared to healthy mice, diabetic rat models can have much higher fasting blood sugar levels. This suggests that the mice in question have diabetes. This analysis gives a broad overview of the severity of diabetic disease in the rat model and the results of the intervention or treatment used (Anthony et al., 2013; Ewenighi, 2015; Shooli et al., 2016; Oh et al., 2010). This analysis aims to evaluate the impact of soursop leaf extract (EDS) and soursop leaf extract nanoparticles (NEDS) on fasting blood glucose levels in diabetic rats. The analysis was carried out at three-time intervals, namely day 0, day 7, and day 14. Descriptive results and statistical analysis were performed for each period.

Based on the results of observations for 14 days, the soursop leaf extract nanoparticle group has better effects when compared to the soursop leaf extract group in terms of lowering blood sugar levels of fasting rats modeled with diabetic conditions. This supports in vitro testing conducted by Badmus et al. (2020), where the study showed that soursop leaf extract made in the form of nanoparticles is effective as an antidiabetic through testing α-Amylase inhibition and α-Glucosidase inhibition in vitro.

Based on the above data, soursop leaf extract made in the form of nanoparticles is confirmed to increase the potential effectiveness in providing biological activity, like other studies that have been conducted previously on various types of biological activity (Jabir et al., 2021; Gavamukulya et al., 2020; González-Pedroza et al., 2021; Meenakshisundaram et al., 2020). Thus, it is known that soursop leaf extract made in nanoparticles can be used as an alternative in the development of antidiabetic drugs in the future to lower blood sugar levels during fasting conditions. However, additional experiments are needed to confirm this.

CONCLUSION

Based on the experimental findings, nanoencapsulation of soursop leaf extract (Annona muricata L.) significantly enhances its antidiabetic efficacy, with the chitosan-based nanoparticle formulation (NEDS) showing a dose-dependent reduction in fasting blood glucose levels in diabetic rats. The highest dose of NEDS (300 mg/kg) demonstrated glucose-lowering effects comparable to the standard drug glibenclamide after 14 days, confirming that nanotechnology can overcome bioavailability limitations of phytocompounds and boost therapeutic potential. This establishes the nano-suspension as a promising drug delivery platform and candidate for future diabetes therapies. Future research should focus on elucidating the precise mechanisms of action, including effects on insulin secretion and key metabolic enzymes, conducting comprehensive pharmacokinetic and pharmacodynamic profiling, and performing long-term safety evaluations. Additionally, process scale-up for consistency and stability is essential to support clinical translation and broader application of this nano-herbal formulation. Addressing these aspects will be critical to validating its effectiveness and safety for human use.

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