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Literature Review

A Literature Review on the Antihyperglycemic Effect of Nanoencapsulated *Etlingera eatior* Extract in Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes mellitus Type 2 (T2DM) is characterized by hyperglycemia due to pancreatic β-cell damage, leading to impaired insulin production. The International Diabetes Federation (IDF) estimates that by 2021, 537 million people worldwide will have T2DM, with projections reaching 783 million people by 2045. In 2023, Indonesia reported a diabetes prevalence of 9.1%, affecting around 25 million people. Nanocarrier-based drug delivery systems show promise in improving diabetes management by enhancing bioavailability and sustaining drug release. This study tested the effectiveness of a nano drug delivery system using nanoencapsulation of *Etlingera elatior* extract in T2DM therapy. *Etlingera elatior* contains flavonoids, polyphenols, saponins, and alkaloids, which exhibit significant antihyperglycemic properties. Nanoencapsulation with biodegradable polymers improves stability and controlled release of bioactive compounds. Using a qualitative document study, data sourced from Google Scholar and Publish or Perish with a range of 2015-2024 were analyzed through NVivo 12 Pro software for MacBook Pro. The findings showed that *Etlingera elatior* effectively lowered blood glucose, improved insulin sensitivity, and protected β-cells, while nanoencapsulation optimized bioavailability. Thus, nanoencapsulation of *Etlingera elatior* represents a promising innovation for diabetes management, potentially improving glucose control and patient outcomes in Indonesia.

INTRODUCTION

The International Diabetes Federation (IDF) reports that the prevalence of Type 2 Diabetes Mellitus (T2DM) worldwide is estimated at 537 million, of which 9.3% of people aged 20-79 years in 2021 and about 747,000 people died in 2021[1]. The prevalence of T2DM is

expected to increase with age to 19.9% or 111.2 million people aged 65-79 years[2]. The number is expected to increase to 643 million people in 2030 and 783 million people in 2045[3]. In Indonesia, the Basic Health Research (Riskesdas) reported the prevalence of T2DM to be around 9.1% or 25 million people in 2023[4]. The data on the increase in T2DM mainly occurs due to an increase in blood glucose levels (hyperglycemia) in patients, so it is necessary to improve disease management of type 2 diabetes mellitus[5].

The management of T2DM generally involves the administration of synthetic antidiabetics such as metformin which serves as one of the main methods to treat elevated sugar levels in the body[6]. However, the use of synthetic antidiabetics has several side effects such as severe hypoglycemia, liver disorders, kidney damage and lactic acidosis, which are often caused by improper dosage, interactions with other drugs, and underlying medical conditions[7]. In addition, reinforced by research by Hutahean, (2020) reported that the available synthetic anti-diabetes treatment can be said to be quite expensive, and also the treatment of diabetes mellitus requires long-term therapy[8]. From these problems, some people turn more to non-medical (herbal) therapy as a complementary therapy to antidiabetic drugs[9]. Research by Dewi et al., (2024) reported that there was a significant relationship between the provision of complementary therapy in the form of herbal extract supplementation in reducing blood sugar levels in diabetic patients with a value of p=0.000 (p<0.05)[11]. Seeing the number of people who turn to non-medical treatment, it is necessary to optimize the use of plants that contain medicinal compounds.

One of the herbal plants utilized by the Indonesian people is kecombrang (*Etlingera elatior*). Choiriyah, (2020) reported that ethanol extract of kecombrang flowers can be used as an antihyperglycemic by inhibiting α-glucosidase enzyme and α-amylase enzyme so that it can delay carbohydrate absorption and reduce sugar absorption after eating so that it plays a role in reducing blood glucose levels. Ethanol extract of kecombrang flowers at a dose of 25µl/ml is more effective in lowering blood glucose than akarbosa[13]. Research by Aritonang, Farabi and Puspodewi, (2023) reported that there was a significant decrease in blood glucose after giving kecombrang flower extract to test animals with a test group with a dose of 100mg/Kg BB showing the highest decrease with a percentage of 59.52% with a value of p <0.05[14].

Several studies have reported that kecombrang content has bioactive compounds that can contribute to glucose control[15]. The utilization of kecombrang extract is still limited and the lack of research that explores its maximum potential use, especially in the context of hyperglycemia[16]. The mechanism of action of the bioactive components in kecombrang cannot work optimally in the digestive tract because these bioactives have characteristics such as low solubility, rapid degradation, low bioavailability, and are quickly damaged by the influence of the digestive tract environment so that they must be protected with polymer stabilizers that can protect these

bioactive components[17]. Thus, nano drug design innovated in the form of nanoencapsulation containing kecombrang (*Etlingera elatior*) extract is expected to be an alternative solution and breakthrough in improving therapeutic properties, reducing morbidity, and having high efficacy[18]. Based on the background description above, the authors are interested in conducting research on "Effectiveness of Nanoencapsulated *Etlingera elatior* Extract as Antihyperglycemia Therapy in Type 2 Diabetes Mellitus: Literature Review".

METHOD

The research employed a qualitative method using coding techniques, supported by NVivo 12 software. A literature review approach was applied, focusing on studies published between 2015 and 2024, particularly those related to nanoencapsulation formulation to support the development of conceptual ideas. The research process was carried out in several stages. First, a literature search was conducted using the Publish or Perish software and Google Scholar, with keywords including *kecombrang*, *type 2 diabetes mellitus (DMT2)*, and *nanoencapsulation*. Second, nodes were created to form thematic structures; this was done manually by thoroughly reading each selected article and summarizing its content in alignment with the research problem. Finally, a concept map was constructed to visualize the relationships among emerging themes and to support further analysis. After determining the nodes in the formation of themes, researchers can visualize the results of research based on the themes that have been made. The concept map in this study is listed in Figure 6.

LITERATURE REVIEW

Diabetes Mellitus Type 2

Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders worldwide. Diabetes is the parent of other diseases such as hypertension, heart stroke, kidney failure, therefore it is known as the mother of disease. T2DM is a chronic metabolic and inflammatory disease accompanied by hyperglycemia, insulin secretion dysfunction, and insulin resistance. T2DM is a manifestation of metabolic disorders with symptoms of dyslipidemia, hypertension, and obesity. This disease is called non-insulin dependent diabetes mellitus (NIDDM) because insulin work is less effective. Antihyperglycemia is a treatment that is very much needed for diabetes sufferers, it is known that the cost of treatment is getting higher, so it is recommended to use herbs as an alternative treatment. One of the promising herbs is torch ginger extract (*Etlingera elatior*), which has been shown to have antihyperglycemic properties through various mechanisms, including reducing insulin resistance and regulating glucose metabolism. The use of

torch ginger as an additional therapy can provide significant benefits for patients with type 2 diabetes mellitus, which is reinforced by research by Aritonang, Farabi and Puspodewi, (2023) reporting that administration of torch ginger flower extract has the potential to lower blood glucose with a p value<0.05[14]. However, the bioavailability of active compounds in torch ginger extract is often low, so nanoencapsulation is a promising strategy to increase therapeutic effectiveness. Nanoencapsulation can increase the stability and solubility of bioactive compounds, as well as encourage controlled release in the body, so that torch ginger extract can protect against degradation and increase absorption in the digestive tract, which can increase the concentration of active compounds and reach systemic circulation [19].

Kecombrang

Kecombrang (*Etlingera elatior*) is often called torch ginger because the shape of the flower resembles a torch and its color is red, included in the Zingiberaceae family. Research conducted on flowers, stems, rhizomes, and leaves of kecombrang shows that there are phytochemical compounds of alkaloids, saponins, tannins, phenolics, flavonoids, triterpenoids, steroids, and glycosides that play an active role as antibacterials and antioxidants[20]. In addition, Kecombrang is known to have pharmacological effects as antihypertensive, antioxidant, antitumor, anticytotoxic, anticancer, antiaging, larvicidal and antihyperglycemic[21].

Flavonoid

Antihyperglycemia from ethanol extract of kecombrang flowers is due to the presence of secondary metabolite compounds such as flavonoids (Figure 2.). There are several flavonoids in kecombrang that function as antihyperglycemic, namely quercetin (Figure 3), kaempferol (Figure 4), and kaempferol-3-O-glucosidase (Figure 5). The mechanism of action of flavonoids that can be used as antihyperglycemic is by inhibiting the enzyme glucosidase or amylase which causes the absorption of carbohydrates and sugar after eating to be delayed so that blood glucose uptake is reduced. Another mechanism of flavonoids playing a role in lowering blood sugar levels is by inhibiting phosphodiesterase (PDE), which causes an increase in cAMP (Cyclic Adenosine Monophosphate) levels in pancreatic beta cells[22].

Flavonoids have protective properties on pancreatic beta cell damage as insulin producers and can increase insulin sensitivity. This will stimulate insulin secretion through the Ca pathway and increase cAMP will close the K + ATP channel in the beta cell plasma membrane. Then the membrane depolarization occurs and the Ca channel will open so that Ca 2+ ions enter the cell and insulin secretion by pancreatic beta cells will occur. The study reported that flavonoid consumption at a dose of ± 25 µl/ml showed significant results in reducing blood sugar levels with

a p value of <0.05[23].

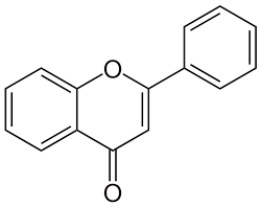

Figure 1. *Structure of flavonoid compounds*

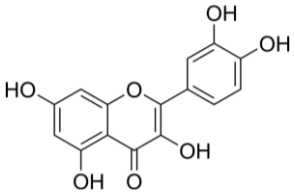

Figure 2. *Structure of quercetin compound*

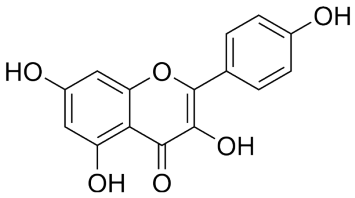

Figure 3. *Structure of kaempferol compound*

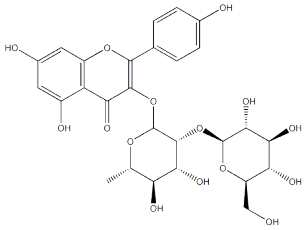

Figure 4. *Compound structure of kaempferol-3-O-glucosidase*

Chlorogenic Acid

The content of secondary metabolite compounds in kecombrang leaves is dominated by chlorogenic acid compounds. Chlorogenic acid (CGA) compounds contained in kecombrang (*Etlingera elatior*) extract have shown potential as antihyperglycemia agents in patients with type 2 diabetes mellitus (T2DM). The content of chlorogenic acid secondary metabolite compounds plays a role in glucose metabolism by improving cellular mechanisms related to glucose uptake into cells that inhibit the activity of alpha-glucosidase enzymes, increase the concentration of Glucose-Dependent Insulinotropic Peptide (GIP), and activate AMP-activated Protein Kinase (AMPK)[18]. This results in the expression and translocation of GLUT-4 which can increase glucose uptake in peripheral tissues and can also inhibit hepatic glucose 6-phosphatase activity so that glucogenesis in the liver decreases[24].

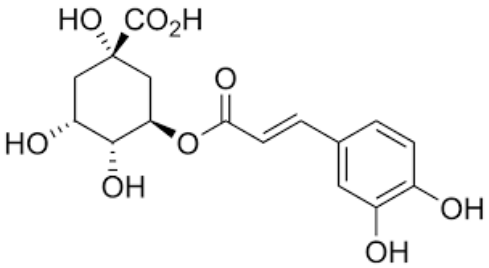

Figure 5. *Chlorogenic acid (CGA) compound structure*

Nanoencapsulation

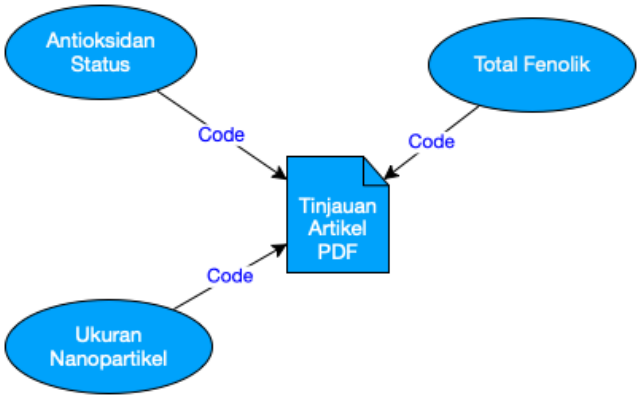

Figure 6. *NVivo Analysis Code Nanoencapsulation article review*

The research report showed that kecombrang nanoencapsulated had an antioxidant activity level of up to 32.165% which is close to 50% of the total measurement based on IC50 [25]. From the total phenolics, it was also explained that nanoencapsulation was able to keep the total phenolics between the range of 216.21 to 289.86mg/100g. Determination of total phenolics can help in new drug development and drug standardization. The size of nanoparticles also varies, it can be determined in the reference article, namely (<1000nm) including the range 134.7-193.1 nm because it can maintain the stability of phenol compounds contained in processed herbal plants[26]. In addition, it is also reinforced in the research of Zubaydah et al. (2023) that particle sizes of 14.56 and 13.8 nm can also be done, because the droplet size in the <100n range will be thermodynamically stable so that the absorption and biovailablity of herbal compounds increases. The nano size of 312.7nm in the study of Wahjuni et al. (2024) with a reference nano size of 200 to 300 nm is also considered suitable for passing through glomerular filtration[27].

Encapsulation is a process in which small particles of material are encapsulated in a wall material to form a capsule[28]. Encapsulation methods were developed to protect bioactive components (polyphenols, micronutrients, enzymes, and antioxidants) from adverse environments so as to control release at the desired target[29]. Nanoencapsulation is defined as a technology that encapsulates or encapsulates a substrate in miniature and refers to an active compound surrounded by a polymer membrane as a wall to protect the active compound. Nanoencapsulation is carried out through the formation of 1-1000 nm particles with active ingredients inside[30]. In drug delivery systems, nanoencapsulation acts as a carrier by dissolving, enveloping, encapsulating, or attaching drugs in their matrix. Nanoencapsulation has many functions, one of which is to deliver functional materials to reach the desired location. The principle of making nanoencapsulation with this method is the occurrence of ionic interactions between the positively charged amine groups in chitosan and the negatively charged polyanions. Nanoencapsulation technology is made by an ionotropic gelation process between the negative

charge of sodium tripolyphosphate (STPP) and the positive charge of the amine groups in chitosan[31]. There are several nanoencapsulation manufacturing techniques that can be carried out, including: emulsification method, coacervation, inclusion complex, two-step desolvation, nanoprecipitation, and supercritical fluid method. Nanoencapsulation can improve the stability and solubility of bioactive compounds, as well as facilitate controlled release in the body, so that the kecombrang extract can be protected from degradation and increase absorption in the digestive tract, which can increase the concentration of active compounds and reach systemic circulation[19].

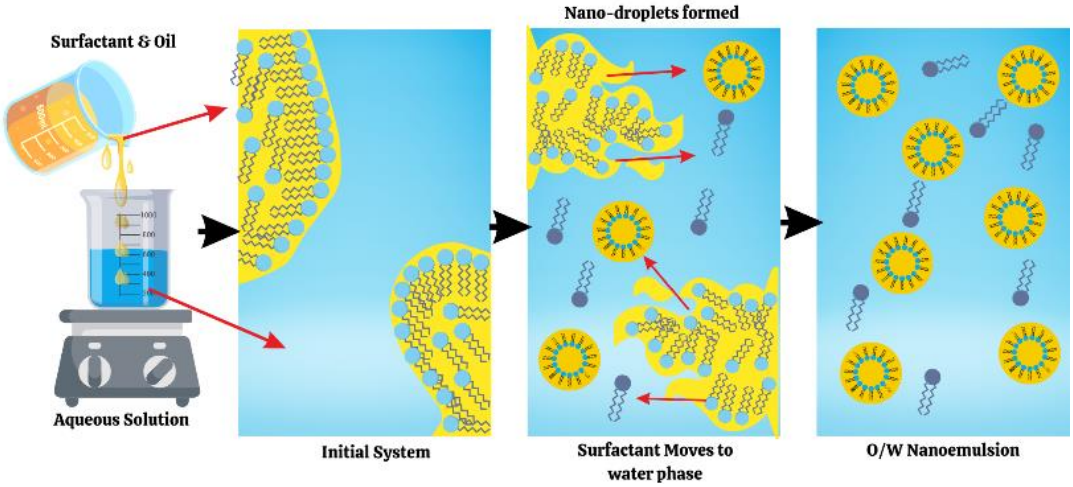

Figure 7. *nanoencapsulation manufacturing technique using emulsification method*

CONCLUSION

Based on the reviewed literature, *Etlingera elatior* extract exhibits significant potential as an antihyperglycemic agent, primarily due to its rich profile of bioactive compounds and its ability to modulate key pathways in glucose metabolism. The application of nanoencapsulation technology not only enhances the extract's physicochemical stability but also improves its gastrointestinal absorption and overall bioavailability. These findings indicate that *Etlingera elatior* could serve as a promising complementary therapeutic strategy for the management of type 2 diabetes. However, to fully realize its clinical potential, future research should focus on optimizing nanoformulation parameters, conducting comprehensive in vivo studies, and initiating well-designed clinical trials to assess safety, efficacy, and long-term benefits in human populations specialized as a complementary therapy in diabetes care.

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