

Conference Paper

Scoping Review: Potential of Bekul Fruit (*Ziziphus jujube* Mill.) as an Antidiabetic Agent in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by high blood glucose (hyperglycemia) caused by damage or abnormalities in insulin production. Pharmacological therapy used as a treatment for diabetes mellitus in some patients has adverse side effects on the body, thus encouraging exploration to use natural ingredients as an alternative therapeutic source in reducing blood glucose. Therefore, a thorough review is needed to summarize scientific data and investigate the potential use of natural ingredients bekul fruit (*Ziziphus jujube* Mill.) in its role as an antidiabetic agent. This study used a scoping review with 4 databases: Pubmed, ScienceDirect, DOAJ and Google Scholar. The results of the scoping review of 5 scientific articles found that bekul fruit (*Ziziphus jujube* Mill.) is proven to have bioactive content that is rich in antioxidants such as phenolic/polyphenolic compounds (ferulic acid, caffeic acid, chlorogenic acid), flavonoids (quercetin, rutin, catechin), phytosterols, and inulin which have the potential as antidiabetic agents with different mechanisms of action in reducing blood glucose levels. Conclusion: bekul fruit (*Ziziphus jujube* Mill.) has the potential to be an alternative nutraceutical diet therapy in patients with diabetes mellitus.

Keywords: Bekul fruit, Ziziphus jujube Mill., bioactive compounds, type 2 diabetes mellitus

Introduction

The progress of this modern era has resulted in changes in people's lifestyles. Currently, people more often consume instant foods, foods that are high sugar and fat, but rarely consume fruits, vegetables and do less physical activity (Hariawan et al., 2019). This can trigger an increase in blood glucose and cholesterol levels, leading to overweight (obesity) and associated diseases such as diabetes mellitus (Wondmkun, 2020).

Diabetes mellitus is a metabolic disorder of carbohydrates, fat, and proteins characterized by high blood glucose levels (hyperglycemia) caused by damage or abnormalities in insulin production so that insulin cannot work optimally (Harreiter & Roden, 2023). As quoted by the International Diabetes Federation (IDF), the prevalence of people with diabetes in Indonesia reached 19.47 million in 2021 and is estimated to increase by 47% to 28.57 million in 2045 (International Diabetic Federation, 2021).

Type 2 diabetes mellitus is one of the most common diseases in Indonesia (Kementerian Kesehatan RI, 2022). The risk factors that cause type 2 diabetes mellitus are due to the interaction between genetic and environmental factors (Gudjinu & Sarfo, 2017). These environmental factors

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include diet and nutrition, overweight/obesity, age, psychological stress, oxidative stress, glucotoxicity, and lipotoxicity, decreased endoplasmic reticulum function, and consumption of drugs that can trigger an increase in blood glucose (Ceriello & Prattichizzo, 2021).

Treatment of diabetes mellitus can use two therapies, namely pharmacological therapy and non-pharmacological therapy (Soelistijo et al., 2021). Pharmacological therapy uses drugs and insulin, either orally or injected in mild to severe doses (Feingold, 2020). However, the effects of this insulin therapy treatment can cause patients to have hypoglycemia, increase body weight and cause gastrointestinal disorders (Schalliol et al., 2019). This encourages exploration of non-pharmacological treatments, namely using natural ingredients as an alternative therapeutic source to reduce blood glucose (Radwan et al., 2020).

Treatment using natural ingredients in diabetes mellitus, also known as complementary alternative medicine (CAM) is growing very rapidly (Loren et al., 2018). One of the plants that have health benefits and can be used as an anti-diabetic agent is bekul fruit (*Ziziphus jujube* Mill.) (Yazdanpanah et al., 2017). Bekul fruit (*Ziziphus jujube* Mill.) is usually found and thrives in dry areas with low rainfall. Bekul fruit (*Ziziphus jujube* Mill.) is known by various names in each region, such as in the Java/Sundanese area known as Widara, Rangka for the Bima area, Kalangga for the Sumba area and Bekul for the Bali area, and Kom for the Kupang area (Raharjeng & Masliyah, 2020). Considering that bekul fruit (*Ziziphus jujube* Mill.) grows wild in several areas, public knowledge about the benefits of bekul fruit (*Ziziphus jujube* Mill.) is lacking, so research needs to be carried out to explore the potential of bekul fruit extract (*Ziziphus jujube* Mill.) as a therapy for diabetes mellitus.

Material and Methods

Protocol design

The design of this review uses a literature scoping review method that refers to Arksey & O'Malley's 5-step framework. The results of this review are reported by PRISMA SR (priority reporting items for systematic reviews and meta-analysis extension for scoping reviews) (Westphaln et al., 2021).

Eligibility criteria

The inclusion criteria in this review were: 1) Full-text articles with national or international reputation, 2) Articles published in 2015 - 2024, 3) RCT research design, 4) Research articles have several items, namely: a) Reference (Title, author, year of publication, index), b) Type of intervention, c) Bioactive substance component, d) Research design (design, method, type of treatment), e) Research results.

Sources of information

Article identification was done by searching data using electronic databases, including Pubmed, ScienceDirect, DOAJ, and Google Scholar. These four databases were chosen because they focus on nutrition and medical science to the objectives of the review.

Search strategy

Search and selection of articles based on the keywords "(bekul fruit OR *Ziziphus jujube* Mill.) AND (bioactive components OR nutraceutical) AND (antidiabetic OR diabetic OR diabetes mellitus) AND (RCT OR Randomized Controlled Trial).

Results and Discussion

Source of evidence

A total of 778 articles were identified through database searches (Pubmed 53, ScienceDirect 124, DOAJ 16, and Google Scholar 585). Of the 778 articles, 715 were eliminated during the initial assessment based on title and abstract, leaving 64 articles found to potentially match the topic of

the scoping review. A total of 9 articles were removed due to duplication, leaving 55 articles. Then, 37 articles were excluded based on study design, leaving 18 articles. Eligible articles based on the inclusion criteria were 11 articles, of which 6 articles were excluded because the findings did not match the purpose of the scoping review, leaving only 5 articles for analysis. Figure 1 shows the PRISMA flowchart detailing the justification for study exclusion.

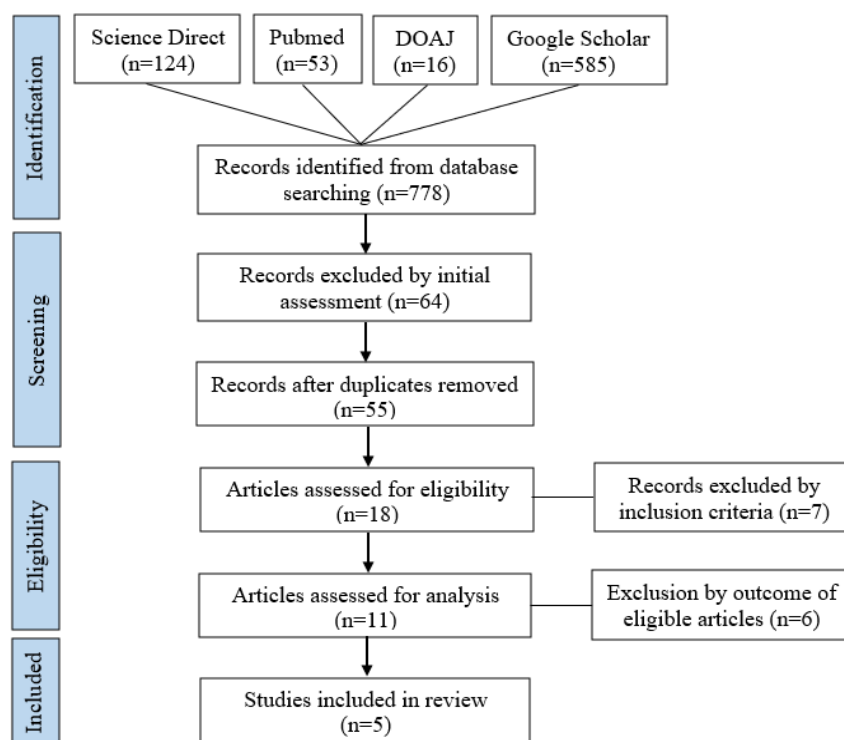


Figure 1. PRISMA flowchart

Synthesize results

After screening many articles, the results were five articles that met the criteria. The articles provide evidence regarding the effectiveness of bekul fruit (*Ziziphus jujube* Mill.) as an antidiabetic agent. The summary results of the research are shown in Table 1:

Table 1. Summary of studies by the criteria

Title	Intervention	Bioactive Compounds	Research Design	Research Results	Reference
Efek Protektif Bekul Bali (<i>Ziziphus Jujuba</i> Mill.) Terhadap Skor Kerusakan Pankreas dan Histopatologi Pulau Langerhans Tikus Terinduksi Diet Tinggi Lemak	Bekul fruit extract (<i>Ziziphus jujuba</i> Mill.)	The flavonoid compound is quercetin.	Design: Quantitative Methods: Experiment Sample: High fat diet induced diabetic male wistar rats Treatment: Bekul fruit extract low dose 200 (mg/kgBB), medium dose 400	Bekul fruit extract can significantly reduce the score of pancreatic damage degree at the best dose of 800 mg/kgBB	(Pramartha et al., 2022)

To be continued...

Effect of <i>Ziziphus Jujube</i> on Cardiometa-bolic factors and systemic inflammation in type 2 diabetic patients: A randomized controlled trial	<i>Ziziphus Jujube</i> dry Iran variety	Inulin, cate-chins, phe-nolic com-pounds (caf-feic acid and chlorogenic acid), rutin	(mg/kgBB), and 800 mg/kgBB). Design: Quantita-tive Methods: Quasi Ex-perimental Sample: Type 2 Di-abetes mellitus pa-tients Treatment: Dried <i>Ziziphus Jujube</i> dose 30 gram/day.	Dried <i>Ziziphus Jujube</i> can sig-nificantly re-duce TG, TC, LDL-C, HbA1c, hs-CRP, and IL-6.	(Farhadneja d et al., 2022)
The effect of dried <i>Ziziphus ju-jube</i> on glycemic control, lipid pro-file, Apo-proteins and hs-CRP in pa-tients with type 2 diabetes melli-tus: A random-ized controlled clinical trial	<i>Ziziphus Ju-jube</i> dry Iran variety	Saponins, phytosterols	Design: Quantita-tive Methods: Quasi Ex-perimental Sample: Type 2 Di-abetes mellitus pa-tients Treatment: Dried <i>Ziziphus Jujube</i> dose 30 gram/day.	Dried <i>Ziziphus jujube</i> reduce body weight, BMI, serum tri-glyceride, se-rum insulin, HOMA-IR, ApoB100, and hs-CRP. In addi-tion, it in-creased QUICKI, ApoA-I and HDL-C val-ues	(Irannejad niri et al., 2021)
Effect of <i>Ziziphus jujube</i> Fruit Infu-sion on Lipid Profiles, Glycae-mic Index and Antioxidant Sta-tus in Type 2 Dia-betic Patients: A Randomized Controlled Clinical Trial	Infus <i>Ziziphus Jujube</i> Fruit (ZJF) Iran Va-riety	Saponins, In-ulin, Phy-tosterol, phe-nolic com-punds (ferulic acid), cate-chins and ru-tin.	Design: Quantita-tive Methods: Quasi Ex-perimental Sample: Type 2 Di-abetes mellitus pa-tients Treatment: ZJF in-fusion 300 ml/day (10 g of ZJF pow-der brewed in 100 ml of boiling water, given three times per day).	ZJF infusion can significantly re-duce HbA1c, TC, LDL-C, TC/HDL-C and LDL-C/HDL-C. ZJF infusion can increase TAC and decrease MDA but not significantly.	(Yazdanpan ah et al., 2017)
Hypoglycemic ef-fects of three Ira-nian edible plants; jujube, barberry and saffron: Cor-relation with se-rum adiponectin levels	<i>Ziziphus Ju-juba</i> (ZJ), <i>bar-beris vulgaris</i> (BV), <i>crocus sativus</i> (CS)	<i>Ziziphus ju-jube</i> (ZJ) con-tains flavo-noid specifi-cally querce-tin.	Design: Quantita-tive Methods: Experi-ment Sample: STZ-in-duced diabetic male SD rats dose 60 mg/kgBB Treatment: ZJ, BV, and CS were re-spectively given doses of 25 mg/kg and 100 mg/kg.	Rats treated with ZJ had an increase in HDL. ZJ, BV, and CS can improve HDL levels and serum glucose in diabetic rats by increasing adiponectin.	(Hemmati et al., 2015)

Summary of Evidence

This scoping review research discusses the potential of bekul fruit (*Ziziphus jujube* Mill.), which focuses on the content of bioactive or nutraceutical substances as antidiabetic agents. Based on the search results, the content of bioactive compounds found in bekul fruit (*Ziziphus jujuba* Mill.) is flavonoids, phytosterols, phenolic compounds, and inulin, which are antioxidants and have the potential to be antidiabetic agents for type 2 diabetes mellitus.

Flavonoids as therapy for diabetes mellitus

Flavonoids are the largest group of phenol compounds found in nature, including in plants such as bekul fruit (*Ziziphus jujube* Mill.) (Hemmati et al., 2015). Flavonoids are antidiabetic compounds because they can reduce blood glucose levels by acting as inhibitors of the enzymes α -glukosidase, maltase, α -amylase and can stimulate glucose uptake in muscles through GLUT-4 regulation (Lim et al., 2022). Flavonoids known to be present in bekul fruit (*Ziziphus jujube* Mill.) are catechins, quercetin, and rutin. Research conducted by Farhadnejad et al. (2022) shows that the catechin and routine content in *Ziziphus jujube* can significantly reduce triglycerides, total cholesterol, LDL-C, HbA1c, hs-CRP, and IL-6. Catechins' role as an antidiabetic is to activate AMPK, which then stimulates GLUT-4 to increase glucose absorption into muscle cells, adipose tissue, and the liver (Miao et al., 2021). The mechanism of the rutin antihyperglycemic effect is by reducing carbohydrate absorption in the small intestine, inhibiting tissue gluconeogenesis, increasing tissue glucose uptake, stimulating insulin secretion from beta cells, and protecting Langerhans pancreas from degeneration (Ghorbani, 2017).

The results of other studies showed that the administration of *Ziziphus jujube* Mill. extract containing quercetin was able to reduce the damage score of the pancreas at the best dose of 800 mg/kgBB (Pramartha et al., 2022). Quercetin has a mechanism of action in diabetes mellitus by reducing lipid peroxidation, stimulating GLUT 4 translocation and its expression in skeletal muscle, improving oxidative stress markers and inflammation in adipose tissue such as Nrf2, heme oxygenase-1, and NFkB, increasing antioxidant enzyme activity (such as SOD, GPX, and CAT), inhibiting GLUT 2 so as to reduce intestinal absorption of glucose and fructose (Ansari et al., 2022).

Phytosterols as therapy for diabetes mellitus

In research conducted by Yazdanpanah et al. (2017) and Irannejad Niri et al. (2021), phytosterol bioactive compounds were found in the fruit of *Ziziphus jujube* Mill. Phytosterols are a class of steroid-group compounds that can be found in plants and have a structure similar to cholesterol. The presence of phytosterols in *Ziziphus jujube* Mill. is able to lower cholesterol levels by inhibiting intestinal cholesterol absorption (Prasad et al., 2022). The content of phytosterol compounds in *Ziziphus jujube* Mill. is proven to be able to reduce body weight, BMI, serum triglyceride levels, serum insulin, HOMA-IR, ApoB100, hs-CRP, increase QUICKI values, ApoA-I, and HDL-C (Irannejad niri et al., 2021). The mechanism of action of phytosterols as antidiabetics is that they can stimulate the pancreas to produce insulin by inhibiting the work of glucose-6-phosphatase in the liver, so as to reduce glucose levels in the body (Prasad et al., 2022).

Phenolic compounds as therapy for diabetes mellitus

Phenolic compounds or polyphenols are compounds that have hydroxyl groups and are most abundant in plants (Chen et al., 2018). Polyphenols have many phenol groups in their molecules and a broad spectrum with different solubilities and show many biological functions, such as protection against oxidative stress (Rudrapal et al., 2022). Phenolic compounds have many health benefits, such as being anti-microbial, anti-cancer, anti-diabetes, anti-inflammatory, and anti-oxidant, with the result that they are often associated with therapy for degenerative diseases (Gothai et al., 2016).

The main phenolic compound in *Ziziphus jujube* Mill. is ferulic acid which can affect glucose metabolism and is hypoglycemic by inhibiting α -glycosidase activity and decreasing hepatic

glucose production with assist the glucose transporters (Yazdanpanah et al., 2017). In another study, it was found that other phenolic compounds were contained in *Ziziphus jujube* Mill. such as caffeic acid and chlorogenic acid which can act as a balancing agent for increased oxidative stress and attenuate pro-inflammatory status in diabetes mellitus (Farhadnejad et al., 2022)

Phenolic compounds have antidiabetic activity because of their potential as inhibitors of α -amilase and α -glucosidase enzymes (Kalita et al., 2018). Enzymes α -amilase and α -glucosidase are enzymes that play a very important role in carbohydrate metabolism. Inhibition of the activity of these two enzymes will cause the rate of carbohydrate digestion to slow and glucose production to decrease, so that glucose absorption in the small intestine is minimal and the increase in blood glucose levels (postprandial) can be prevented or reduced (Aleixandre et al., 2021).

Inulin as therapy for diabetes mellitus

Inulin is a form of soluble fiber that cannot be digested by enzymes in digestion because only specific enzymes can digest inulin (Miao et al., 2021). Inulin has the best prebiotic effect compared to others and has several benefits for human health, including improving the performance of the digestive system and reducing blood fat and blood glucose levels (Chambers et al., 2019). A study conducted by Yazdanpanah et al. (2017) proved that the inulin content in the fruit of *Ziziphus Jujube* Mill. was able to significantly reduce HbA1c, total cholesterol, LDL-C, TC/HDL-C, and LDL-C/HDL-C levels. The mechanism inulin acts as an antidiabetic agent is by increasing insulin secretion stimulated by pancreatic cells, improving insulin sensitivity, and increasing gastric viscosity so that it slows digestion and postpones gastric emptying, which will cause a person to not easily feel hungry (Miao et al., 2021).

Conclusion

Bekul fruit (*Ziziphus jujube* Mill.) has the potential to be an alternative nutraceutical diet therapy for patients with diabetes mellitus. This research can be used as a basis for further research and develop the potential of using bekul fruit (*Ziziphus jujube* Mill.) in the treatment or prevention of diabetes mellitus.

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Not applicable.

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