Exploring the Potential of Poguntano Extract on Diabetes Management: Systematic Review and Meta-Analysis

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ABSTRACT

Background: Poguntano (Picria fel-terrae Merr) is a traditional herb commonly used as a blood glucose lowering agent in Indonesia. However, the effectiveness of the herb has not yet been established. Objective: This systematic review and meta-analysis aim to review the hypoglycemic effect of Poguntano extract in lowering plasma glucose levels. Methods: We conducted a literature search using peer-reviewed databases for relevant articles on Poguntano extract in animal models of diabetes. The effect size was pooled using a random effect model. Results: Two animal studies were included in the systematic review and meta-analysis. There was a significant difference in plasma glucose levels between diabetic control and rats treated with Puguntano extract (MD: 28.77; 95%CI: 6.20–51.34; p=0.01). There was no significant difference between non-diabetic control and Poguntano extract. Conclusion: Poguntano extract lowers the blood glucose levels in diabetic rats compared to control.

Keywords: Animal, Diabetes Mellitus, Meta-Analysis, Poguntano.

1. BACKGROUND

Diabetes is a group of metabolic diseases characterized by high blood glucose caused by defects in insulin secretion, insulin action, or both. According to Indonesian 2018 Basic Health Research (Riset Kesehatan Dasar / RISKESDAS), approximately 8.5% of Indonesians suffer from Diabetes Mellitus. Furthermore, risk factors for diabetes are highly prevalent in Indonesians, such as Obesity (21.8%), Overweight (13.6%), and central obesity (31%). (PERKENI) Research has shown that over the years, the global prevalence of diabetes is steadily increasing, especially in low and low-middle-income countries (1).

Diabetes is a particularly debilitating disease due to its various complications and its lifelong drug usage. This means that the economic burden of diabetes comes from both its medical cost (including antidiabetic drugs, insulin, and complication treatments) and its cost on the loss of earnings and productivity. Research has shown that the global economic burden for diabetes is estimated at approximately US$1.3 trillion in 2015 and will climb to US$2.1 trillion in 2030 (2). Diabetes treatment is also particularly expensive, with the annual cost of insulin reaching up to US$300 in several countries (3).

Oral antidiabetic drugs, although effective in controlling blood glucose, have their own disadvantages. Sulfonylureas are associated with a higher incidence of hypoglycemia and weight gain, while SGLT-2 inhibitor is associated with a higher incidence of UTI and weight gain. Furthermore, the first line treatment for type 2 diabetes mellitus, metformin, has been associated with lower efficacy as the disease progresses, causing the need for combination therapy or a switch to insulin (4).

Poguntano (Picria fel-terrae Merr) is a medicinal plant found in North Sumatera and has been traditionally used as a treatment for diabetes, fever, malaria, and cancer. Several pieces of research have shown its hypoglycemic effect in animal studies (5, 6) with little to no side effects and toxicity.

2. OBJECTIVE

Therefore, we conducted this systematic review and meta-analysis to study the impact of Poguntano extract on blood glucose levels and its potential as an antidiabetic agent.
3. MATERIAL & METHODS

3.1. Selection of Study

We conducted a systematic literature search from peer-reviewed journals using databases such as PubMed, Scopus, ProQuest, and ScienceDirect for animal studies on the effect of Poguntano extract on the blood glucose levels. We used the exact same keywords for all the databases as follows: (("Poguntano" OR "Pugun Tano" OR "Pugun Tana" OR (Picria fel-terrae))) AND (diabetes mellitus [MeSH Terms]) AND (diabetes mellitus [SAME Terms]) AND (diabetes mellitus [MESH Terms]) AND (diabetes mellitus [EMTREE Terms]) AND (diabetes mellitus [NLM Terms]).

We limit the searches to studies published in English and Indonesian. We also hand-searched relevant articles from the studies.

We included animal studies that involved diabetic rats and which intervention was Poguntano extract. The study should measure at least one outcome on blood glucose level or outcome related to hyperglycemia (HbA1c, fasting blood glucose, Endothelin-1, etc.).

| Author          | Year Published | Animal Model or Cell Line Details | Poguntano Extract | Outcome                                                                 |
|-----------------|----------------|-----------------------------------|-------------------|-------------|
| Widjaja 2018    | Male wistar rats | Picria fel-terrae Lour. leaves     | 200 mg/kg Oral    | Plasma glucose reduction of 302 mg/dL on the poguntano group, as compared to 62 mg/dL in diabetic control and 386 mg/dL in insulin group. |
| Sumantri I 2018 | Wistar rats, weight of 25-30 g | Picria fel-terrae Lour. leaves    | Oral              | Plasma glucose reduction of 12.58,46.59;17.41 mg/dL respectively for 50,100, and 200 mg/kgBW of poguntano crude extract; as compared to 12.33 mg/dL plasma glucose reduction on glibenclamide group |
| Widjaja S 2017  | Male wistar rats, weighing 150-250 g | Picria fel-terrae Lour. leaves | Oral              | Plasma glucose reduction of 373 mg/dL and 302 mg/dL respectively for 300 mg/kg and 200 mg/kg dose; as compared to 62 mg/dL on the diabetic control and 386 mg/dL on the insulin group |

Table 1. Studies included in the systematic review

3.2. Risk of Bias Assessment

We assessed the risk of bias using SYRCLE’s Risk of Bias assessment for animal studies. The tool divides the risk of bias into 6 domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. We classified the risk of bias as “low”, “moderate”, or “high” according to the result of the 6 domains and whether domains with a high risk of bias have a high probability of influencing the result.

3.3. Data Extraction

We extracted relevant data from the studies, which include study author, year published, animal model or cell line, intervention and comparator, sample size, intervention period, and relevant outcomes. All data extraction and risk of bias assessment were done by two investigators working independently. Discrepancies were solved by discussing the relevant information, and when
an agreement cannot be reached, a third investigator is asked to resolve the issue.

3.4. Quantitative Analysis

All extracted data were analyzed using Review Manager 5.4 (Cochrane Collaboration). The effect size was pooled using a random effect model when high heterogeneity (I² >70%), or a fixed effect model when low heterogeneity. The measure of effect for continuous variables as the mean difference. We set the confidence interval at 95%. We then plot the data on the forest plot.

4. RESULTS

4.1. Study Selection

The result of the systematic literature search identified 46 papers from the databases. 5 studies were sought for full paper after title and abstract screening, and full papers for 2 studies were retrieved. The full paper for the 3 studies was not available and therefore is not included in the systematic review and meta-analysis.

4.2. Included Studies’ Characteristics and Outcome

From the two studies extracted, both studies involved male Wistar rats model of diabetes mellitus. The study by Widjaja et al. involved 4-8 weeks old male Wistar rats which were induced to diabetes using intraperitoneal Alloxane monohydrate injection. The study compared four groups of animals: (1) Control, (2) Diabetic Control, (3) Diabetic rats treated using lantus insulin, and (4) Diabetic rats treated using ethanolic extract of Poguntano. The result of the study shows that poguntano extract group had lower blood glucose at week four after treatment compared to diabetic control (127.33 ± 15.04 vs 312.67 ± 60.01; p<0.001), and had comparable effect with rats treated with insulin (Poguntano vs Insulin: 127.33 ± 15.04 vs 107.67 ± 49.66; p=0.566). Additionally, there were significant differences in Endothelin-1 levels in rats treated with Poguntano extract compared with diabetic control (0.55(0.00-1.27) vs 1.95 (1.78-3.10); p=0.009).

The study by Sumantri et al. involved obese Male Wistar Rats divided into 5 groups: (1) Control, (2) 10mg/kgBW glibenclamide, (3) 50mg/kgBW Poguntano extract, (4) 100mg/kgBW Poguntano extract, (5) 200mg/kgBW Poguntano extract. Then plasma blood glucose was measured at 30-, 60-, 90-, and 120-minutes post administration. The result of the study shows that there is significant difference in blood glucose level at baseline and at 30,60,90, and 120 minutes. In all Puguntano doses (50,100, and 200), there were significantly lower blood glucose levels compared to baseline at 120 minutes. The study characteristic is shown in Table 1.

4.3. Quantitative Analysis

The result of the effect size pooling shows that there was significant difference in blood glucose level between poguntano extract and non-diabetic control (MD: -131.92; 95%CI: -248.23 to -15.61; p=0.03). However, there were significant heterogeneity between the studies (I² = 94%). Elimination of one study to reduce hetero-

| Selection Bias | Widjaja 2018 | Sumantri 2018 | Widjaja 2017 |
|----------------|--------------|---------------|--------------|
| Sequence generation | Baseline characteristics | Allocation concealment |
| Performance bias | Random housing | Blinding |
| Detection bias | Random outcome assessment | Blinding |
| Attrition bias | Incomplete outcome data |
| Reporting bias | Selective outcome reporting |
| Other | Other sources of bias |
| Overall | | | |

Table 2. Risk of Bias Assessment

Figure 1. The forest plot of blood glucose level between poguntano extract and nondiabetic control

Figure 2. The forest plot of blood glucose level between poguntano extract and diabetic control
geneity was conducted. However, heterogeneity is still high. The forest plot of blood glucose level between poguntano extract and nondiabetic control is presented in Figure 1.

There was significant difference in blood glucose level between poguntano extract and diabetic subjects, with subjects treated with poguntano extract having lower blood glucose level compared to diabetic control (MD: 27.60; 95%CI: 6.53–48.67; p=0.01). Additionally, we found no heterogeneity between the studies (I² = 0%). The forest plot of blood glucose level between poguntano extract and diabetic control is presented in Figure 2.

4.4. Risk of Bias Assessment

There were some concerns about the risk of bias for all studies due to the fact that no studies were blinded. Overall risk of bias was moderate for all studies. However, we believe despite the moderate risk of bias, all studies are eligible for this review and further quantitative analysis. Risk of Bias table is presented in Table 2.

5. DISCUSSION

The present study aims to investigate the hypoglycemic effect of Poguntano extract. Two studies were included, and the result of the study shows that diabetic rats treated with Poguntano extract have significantly lower blood glucose compared to control. However, there are no significant difference between poguntano treated rats and normal (control, non-diabetic) rats in terms of blood glucose level.

Poguntano (Pierce fel-terrae) is a traditional herb commonly used in North Sumatera to treat various diseases, including diabetes. Traditionally, people chew on the fresh leaves of the plant in order to reduce their blood glucose level. The herb has also been used for various other purposes. Poguntano decoction has been used traditionally in some parts of Malacca and Philippines to treat helminthiases and colic pain, and ethanolic extract of the herb is traditionally used as an appetite stimulant (6).

The effect of poguntano extract on diabetes mellitus has been studied previously. Lindarto et al. (7) studied the effect of Poguntano on adiponectin receptors in diabetic rats. The result of the study shows that rats treated with Poguntano extract expressed higher Adiponectin receptors compared to control. This might explain the glucose lowering effect of Poguntano extract, which is mediated by resolution of inflammation and subsequently improves insulin sensitivity in these rats.

Syafiril et al. (8) also studied the effect of Poguntano extract on Mitogen-activated protein kinase (MAPK) and glucose transporter 4 (GLUT-4) expression. Poguntano significantly increases GLUT-4 expression in T2DM rat model, meaning that aside from resolving inflammation, poguntano also improves insulin sensitivity through upregulation of GLUT-4 in skeletal muscle.

Our result shows that there is significant difference in plasma glucose level between diabetic control and diabetic rats treated with poguntano extract, with mean reduction of 28.77 mg/dL. This hypoglycemic effect of the extract is also demonstrated in a human clinical trial conducted by Purba et al. (9) showing that 12-week treatment using 100mg Poguntano extract in diabetic patients is associated with lower fasting blood glucose and HbA1c compared to control.

Sumantri et al. (6) also analyzed the safety profile of Poguntano extract in animal models. Even with doses as high as 10,000mg/kgBB, there were no deaths. However, rats treated with high dose Poguntano have reduced movement and were less reactive to stimuli for the first 1-4 hours, after which they returned to normal physiological response. This result shows that Poguntano extract is safe to be administered in animal models. However, the safety profile of the extract in humans should be studied further in clinical trials.

The risk of bias for all studies was moderate. However, this is due to no blinding for the subjects. However, it is unlikely that this affects the result of the studies due to objective assessment of plasma glucose and similar treatment for all groups. Additionally, all the methods are properly mentioned in the studies and there were no methods that likely favored either control or intervention group. Therefore, it is unlikely that the non-blinding nature of the studies significantly affect the result.

Limitation of the study

This systematic review and meta-analysis is not without limitations. Firstly, we only identified two studies eligible for the systematic review and meta-analysis, meaning that the pooled effect size still has a wide confidence interval. Additional studies with larger sample sizes are required to improve the confidence interval. Secondly, the studies included in this meta-analysis are animal studies, meaning that the result of the study might differ in human study. However, one clinical trial on the subject has confirmed the result of the animal study. Nevertheless, additional trials involving larger sample size is warranted to improve the statistical power of the study.

6. CONCLUSION

This meta-analysis shows that poguntano extract is effective in lowering plasma glucose in rat models of diabetes mellitus. However, further clinical trials are required to confirm this effect in human subjects.

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