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Review Article

Effect of Basil Leaf Extract on Diabetes: A Systematic Review and Meta-Analysis

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ABSTRACT

The pharmacological properties of basil (*Ocimum basilicum L.*) have been widely researched for its antidiabetic activity. However, its potency in lowering serum glucose levels is still under investigation. Determination of the effect of basil leaf extract as an antidiabetic drug was the aim of this systematic review. Literature searches were conducted using online databases for peer-reviewed articles on basil extract in diabetic rats. A random effect model was used to pool the effect size. Seven studies were included in this review, and there was a statistically significant difference in plasma glucose levels between the diabetic group and the group with the *Basil* extract intervention. The most significant difference was observed at a concentration of 100 mg/kg (MD: −265.59; 95% CI: 419.49 to 111.69; $p< 0.00001$). Thus, it could be concluded that basil leaf extract can lower blood glucose levels in diabetic animal models.

***Keywords*:** Animal, Diabetes, Meta-Analysis, Basil, *Ocimum basilicum*

Introduction

Diabetes, characterised by prolonged hyperglycaemia, is a chronic metabolic disorder.[1] The 2021 worldwide prevalence of diabetes was estimated to be 10.5%, expected to increase to 12.2% by 2045. Indonesia is among the 10 countries with the highest number of diabetes cases, with a reported 19.5 million people in the nation with diabetes.[2] Indonesian Basic Health Research (Riset Kesehatan Dasar / RISKESDAS) found that approximately 8.5% of Indonesians met the diagnosis criteria for diabetes mellitus.[3] If left untreated, diabetes imposes severe complications to the heart, blood vessels, eyes, kidneys, and nerves[1].

With its estimated global direct health cost of 760 billion USD in 2019 and expected to rise to 825 billion USD by 2030,[4] diabetes is one of the world's leading causes of economic loss, mortality, and disability.

The economic burden is experienced by the patient as well, with costs of care for diabetes with macrovascular complications being three-fold more than for diabetes without complications. The cost of care for microvascular complications is also twice that of the cost of care for diabetes without complications. These increased costs are due to extended hospital stays, increased oral antidiabetic drug and insulin treatment, and more outpatient visits.[5] Current glycemic control agents primarily include chemical agents, such as biguanides, sulfonylureas, and thiazolidinediones, which often result in various undesirable adverse events, including lactic acidosis, weight gain, and hypoglycaemia, that affect the quality of life for patients.[6,7] The efficacy of these compounds also decreases as the disease progresses, requiring combination therapy or a switch to a more potent drug, such as insulin, whose average price has surged over recent years.[8,9]

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Based on those rationales, continuous development in discovering novel antidiabetic drugs that are safe, have similar efficacy, and have fewer side effects is required, especially during pandemics, such as the recent COVID-19 pandemic, where diabetes was closely correlated with COVID-19 morbidity, including hospitalisation, critical illness and mortality.[10] The pharmacological properties of basil (*Ocimum basilicum L.*) have been studied for its various potent effects, including antimicrobial, antioxidant, cardioprotective, anticancer, and antidiabetic effects.[11] It has the potency to inhibit the mobilisation of hepatic glucose and the enzyme for metabolising carbohydrates. This candidate for new antidiabetic drugs also has minimal hepatotoxicity risk and safety for chronic oral administration.[12] This study aimed to establish the effect of basil leaf extract on serum glucose levels and its potential as a novel antidiabetic phytotherapy.

Materials and Methods

Search Strategy

This meta-analysis and systematic review were performed under Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. A systematic literature search of peer-reviewed journals was conducted to identify the effect of basil leaf extract on blood glucose levels using online databases such as PubMed, Scopus, Embase, and EBSCOHost. The search was carried out with the following search terms: (basil and (leaf OR leaves) OR (*basilicum, ocimum* [MeSH Terms]) OR (*basilicums, ocimum* [MeSH Terms]) OR (*0*[MeSH Terms])) and (diabetes OR diabetic* OR (diabetes mellitus[MeSH Terms])). A manual search for relevant articles was also performed.

Inclusion and Exclusion Criteria

We included studies if they: i) involved animals as subject samples with basil extract as the intervention; ii) were written in English or Bahasa Indonesia; and iii) published a full-text article. Studies were excluded if: i) the basil extract was made of parts other than the leaves.

Risk of Bias Assessment

SYRCLE's Risk of Bias tool for animal studies was used to assess the risk of bias. The six domain tools assessed within the risk of bias included selection, performance, detection, attrition, reporting, and

other biases. The risk of bias was classified as "low", "moderate", or "high" based on the six domain results and whether the high-risk domain of bias showed a possibility of biased results.

Data Extraction

A single reviewer completed the data extraction. The data from the studies were extracted, including study author, year published, type of animal model, intervention and comparison, sample size, intervention period, and relevant outcomes. Two independent investigators assessed the risk of bias assessment, and all data were extracted. Discrepancies were solved by examining the extracted data, and a third investigator was involved when an agreement could not be reached.

Statistical Analysis

Review Manager 5.4 (Cochrane Collaboration) software was used to analyse the data. The random effect model for high heterogeneity data ($I^2 > 70\%$) or a fixed effect model for low heterogeneity data was used to pool the effect size. A measure of effect for continuous variables was performed to calculate the mean difference. The confidence interval was set at 95%. The data were plotted as a forest plot.

Results and Discussion

Using the search mentioned above strategy, 363 papers were initially identified, from which 156 duplicates were removed, and nine reports passed the records screen and were retrieved. Seven were eligible to be included in the study for analysis.[13–18] (Figure 1) The primary reasons for exclusion were the unavailability of the full text (n = 1) version and the utilisation of basil seeds instead of the leaf as the intervention (n = 1).

Four of the seven experiments involved administering streptozotocin, and two involved administering alloxan to induce hyperglycaemia. Only one study used dogs as its animal model, and the remaining used mice as their animal models. The intervention duration was between seven days and 13 weeks, with the number of samples in each study ranging between 40 and 72. All studies applied extract from basil leaves, with various extraction methods and modes of administration. The intervention group was compared to the control group with either untreated or intervention with metformin as a widely used antidiabetic agent. All studies showed a decrease in plasma glucose after administering basil leaf extract compared to the control group.

From the seven extracted studies, three[14–16] did not present the numerical data for the plasma glucose change, and one study[13] did not provide the exact intervention dose. Hence, only three articles were included in the forest plot. The study characteristics are shown in Table 1.

The pooled effect size results show a statistically significant difference in plasma glucose level between the control group without treatment and the intervention group with 100 mg/kg sample weight of basil leaf extract (MD: −265.59; 95%CI: −419.49 to −111.69; $p< 0.0007$). Unfortunately, there is a significant heterogeneity between studies (I^2 = 97%). A forest plot of the comparison of blood glucose levels for 100 mg/kg basil leaf extract and the control is presented in Figure 2.

However, at higher extract concentrations (200 mg/kg and 400 mg/kg), no significant difference was observed between the control and intervention groups treated with basil leaf extract. The mean difference was −177.33 mg/dL (95%CI: −466.22 to 111.56; p=0.23) for 200 mg/kg and −179.22 mg/dL (95%CI: −652.33 to 293.89; p=0.46) for 400 mg/kg. Significant heterogeneity was shown between studies (I = 99%) for both doses. The forest plots are presented in Figures 3 and 4.

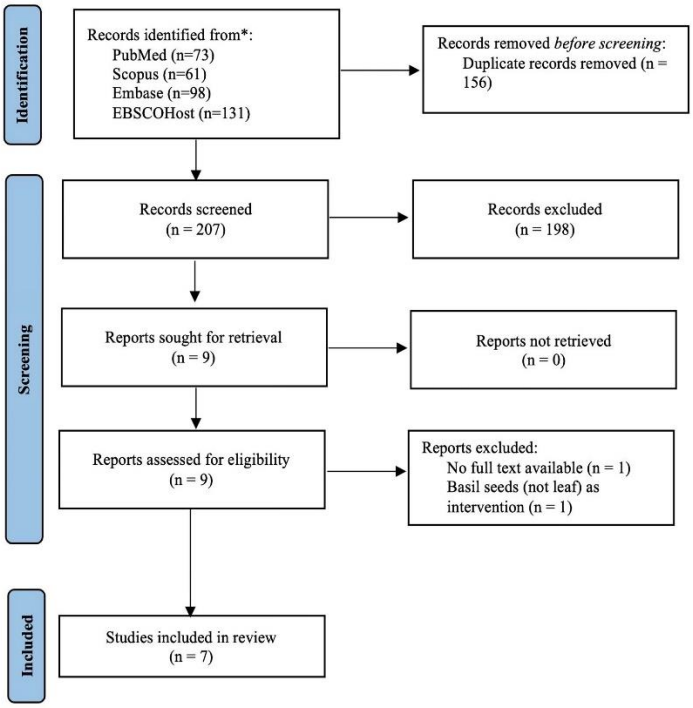

Figure 1: PRISMA flow chart of identified papers, screening, and inclusion for this meta-analysis

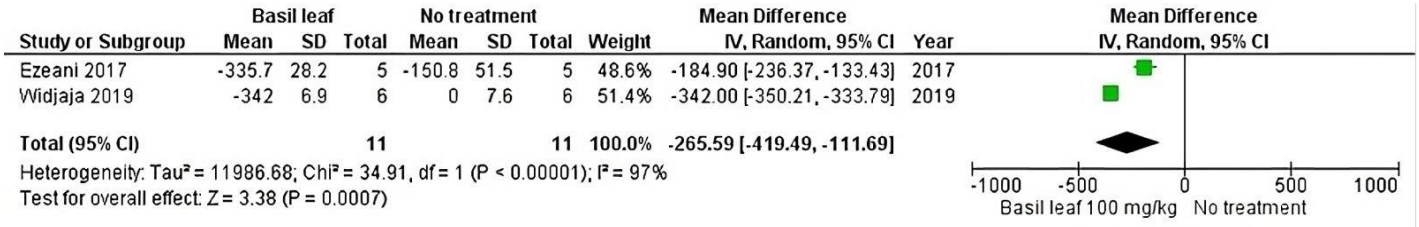

Figure 2: Forest plot of mean difference between 100 mg/kg basil leaf extract and the control sample

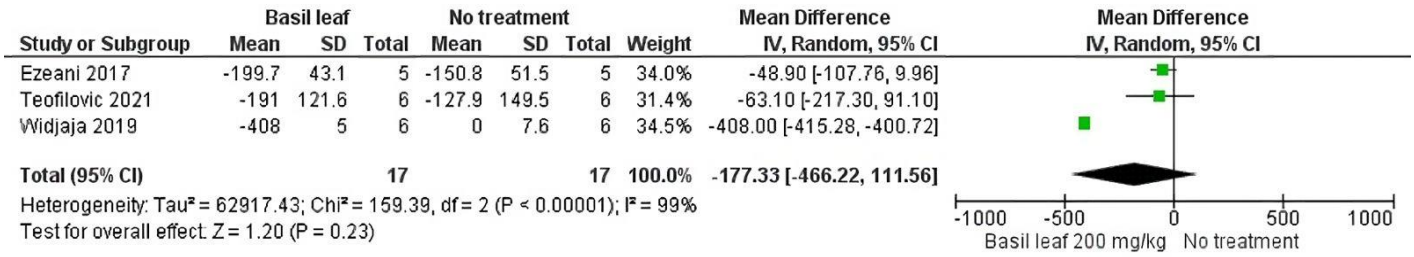

Figure 3: Forest plot of the mean difference between 200 mg/kg basil leaf extract and the control sample

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Table 1: Studies included in this systematic review

Author	Year Published	Animal Model or Cell Line Details			Basil Extract				Comparison	Outcome
		Animal Model; Induction Method	Sample Size	Intervention Period	Sample Used	Extraction Method	Dose	Administration Method		
Ezeani *et al*.[12]	2017	Adult Swiss Albino Wistar *r*ats weighing 100–200 g; induced by intraperitoneal injection of 160 mg/mL alloxan monohydrate + water solution	40 total samples, with each group consisting of six samples	30 days	*Ocimum basilucum L*. leaves	Cold maceration technique in a mixture of dichloromethane: methanol (1:1) for 48 h	100 mg/kg 200 mg/kg 400 mg/kg	Oral	Untreated, 150 mg/kg metformin	Fasting blood glucose: - 100 mg/kg: 335.7 ± 28.2 decline, $p < 0.001$ - 200 mg/kg: 199.7 ± 43.1 decline $p < 0.05$ - 400 mg/kg: 86 ± 100.5 decline, not significant - metformin: 282.4 ±43 decline, $p < 0.01$ - untreated: 150.8 ± 51.5 decline Oral glucose tolerance - 100 mg: 27.8% decline, $p < 0.001$ - 200 mg: 19.2% decline, not significant - 400 mg: 26.4% decline, $p < 0.05$ - metformin: 40.5% decline, $p < 0.01$

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Almalki *et al*.[14]	2019	Adult male Spraque-Dawley rats weighing 200–250 g; intraperitoneal injection of STZ 60 mg/kg in 0.01 M sodium citrate buffer	40 total samples, with each group consisting of 10 samples	6 weeks	*Ocimum basilucum L.* leaves	Hydrodistillation for 4 h in a Clevenger apparatus to extract the essential oil with 1.7% (v/w) yield	60 mg/kg	Intraperitoneal	Untreated, metformin at 500 mg/kg/day	Blood glucose levels significantly decreased with treatment with *O. basilicum* ($p = 0.01$) compared to untreated diabetic rats.
Widjaja *et al*.[21]	2019	Male Wistar rats weighing 150–200 g; intraperitoneal injection of 40 mg/kg of STZ	30 total samples, with each group consisting of five samples	4 weeks	*Ocimum basilucum L.* leaves	Maceration using 96% ethanol	100 mg/kg BW 200 mg/kg BW 400 mg/kg BW	Intraperitoneal	Untreated, metformin at 45 mg/BW	Blood glucose levels: - 100 mg/kg: 131 ± 6.4 (342 ± 6.9 decline) - 200 mg/kg: 123 ± 3 (408 ± 5 decline) - 400 mg/kg: 107 ± 3 (418 ± 8.4 decline) - Metformin: 92 ± 4 (461 ± 6.4 decline) - Untreated: 495 ± 4.6 (0 ± 7.6 decline) No significant difference between treatment groups ($P = 1$) Significant differences between diabetic and treatment groups ($P = 0.00$)

Abdelrahman *et al*.[13]	2020	Rottweiler dogs, 4 months old	45 total samples divided into five groups	8 weeks	*Ocimum basilucum L.* leaves	Powdered dried leaves	0.05% of daily provided food	Oral	Untreated	Serum glucose - Basil: 80.68 ± 5.62 - Control: 116.97 ± 1.11 $p < 0.05$ Serum insulin - basil: 5.36 ± 0.25 - control: 3 ± 0.06 $p < 0.05$
Al-Subhi *et al*.[15]	2020	Adult Sprague Dawley rats weighing 200 ± 5 g; intraperitoneal injection of 50 mg/kg of STZ dissolved in 0.01 M citrate buffer	60 total samples divided into six groups	13 weeks	*Ocimum basilucum L.* leaves	Crude extract (50 g of dry solids) suspended in 100 mL of water	0.5 mg of water extract/1 mL water/day	Oral	Untreated	Serum glucose level significantly decreased with treatment with *O. basilicum* ($p = 0.01$) compared to untreated diabetic rats.
Othman *et al*.[16]	2021	Adult male albino rats weighing 200–220 g were fed HFD for 28 days and then intraperitoneally injected with 40 mg/kg of STZ	42 total samples divided into six groups	4 weeks	*Ocimum basilucum L.* leaves	Ethyl acetate extract	250 mg/kg/day	Not stated	Untreated, metformin at 200 mg/kg/day	Treatment with *O. basilicum* and metformin resulted in considerable decreases ($p < 0.05$ and $p < 0.05$, respectively) in serum glucose and insulin compared to those in untreated samples.
Teofilovic *et al*.[17]	2021	Male Wistar rats weighing 250–300 g; tail injection of alloxan (130 mg/ml)	72 total samples divided into 12 groups	7 days	*Ocimum basilucum L.* leaves	Dry basil extract suspended in water	200 mg/kg BW	Oral	Untreated	Blood glucose: - 200 mg/kg: 190.8 ± 126 decline - saline: 127.9 ± 149.4 decline (not significant compared to the control)

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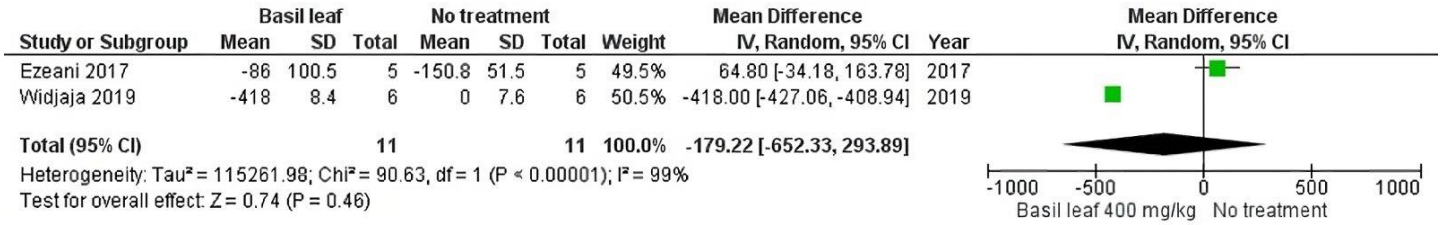

Figure 4: Forest plot of the mean difference between 100 mg/kg basil leaf extract and the control sample

Table 2: Risk of bias assessment

Type of bias	Domain	Ezeani *et al.*[12] 2017	Almalki *et al.*[14] 2019	Widjaja *et al.*[21] 2019	Abdelrahman *et al.*[13] 2020	Al-Subhi *et al.*[15l], 2020	Othman *et al.*[16] 2021	Teofilovic *et al.*[17] 2021
Selection Bias	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							

Green colour: low risk of bias; yellow colour: unclear risk of bias; red colour: high risk of bias

Animal intervention studies are more prone to biases and methodological invalidity than randomised controlled trials. SYRCLE's risk of bias assessment tool was implemented to improve the critical appraisal of evidence from animal studies included in this review. When performing a risk of bias analysis of the seven animal studies, it was revealed that all studies showed a low risk of bias concerning selective reporting (bias reporting). All but one study had a low risk of attrition bias, with the one considered moderately biased. The detection bias in all studies was considered moderately biased. The performance bias assessment results vary. Concerning the blinding domain, a high bias risk was found in two studies, whereas the bias risk of the others was low. Four of seven studies were considered moderately biased regarding random housing, whereas the others have a low risk of bias. Regarding selection bias, five of seven have a high risk of bias in sequence generation, five have a moderate risk of bias in baseline characteristics, and six have a moderate risk of bias in allocation concealment. The risks of bias for the seven studies are presented in Table 2.

This study aimed to determine the plasma glucose-lowering effect of basil leaf extract. Five studies were included, yielding favourable results towards basil leaf extract as a novel antidiabetic drug compared to controls in animal studies. A significant difference was found in the plasma glucose decrease between samples receiving the basil leaf extract and the untreated control.

Basil (*Ocimum basilicum*), a native plant from Central Africa to Southeast Asia, has been cultivated worldwide. Traditionally, basil has been used as a culinary herb and medicinal plant in treating coughs, headaches, diarrhoea, constipation, warts, and worms. The essential oil derived from this plant has been investigated for its antimicrobial, antioxidant, cardioprotective, anticancer, and antidiabetic properties.[19] Numerous studies to explain the pathways of basil in producing hypoglycaemic effects are ongoing. Hannan et al. showed that basil leaf extract demonstrates an insulin-secretory effect, enhances insulin secretion from isolated islets and the pancreas, and modulates intracellular calcium.[20,21] The extract also enhances physiological pathways on pancreatic β-cells, indicating its insulinotropic potency.[22] Ezeani et al. showed that basil leaf extract could inhibit α-amylase and α-glucosidase, which suppress carbohydrate metabolism and the consequent glucose release from the small intestine lumen, leading to its postprandial anti-hyperglycaemic effect.[12]

Basil leaf extract exhibited safety and similar efficacy when administered both acutely and chronically. No significant increase in biochemical markers (SGOT, SGPT, ALP, and Gamma GT) was observed after the extract's acute, subacute, or chronic administration. Histological liver, kidney, lymph, lung, and pancreas biopsy showed normal results consistent with the markers. Hence, this provides safety evidence that basil extract does not cause any harm after chronic administration. A moderate risk of bias was found in all studies. The

allocation of sequences in most studies could be better generated and applied. They were poorly reported, providing a high risk of selection bias. However, an objective assessment of blood glucose was performed in all intervention/control groups, making this risk of bias unlikely to influence the results. Moreover, procedures that needed to be conveyed throughout all studies, from inducing diabetes to animal culling and sample collection, have been adequately addressed. The blinding of the samples throughout intervention and collection was also described. Hence, inadequate randomisation in the studies might not significantly affect the results.

There are certain limitations to this systematic review and meta-analysis. Only three studies eligible to be plotted were successfully identified for the systematic review and meta-analysis, and the pooled effect size still has a wide confidence interval. Thus, additional articles with a larger sample size might be required to narrow the confidence interval to improve the statistical power of this systematic review and meta-analysis.

Conclusion

This meta-analysis showed that basil leaf extract effectively lowered blood glucose in diabetes-induced animal models. Further exploration of its active constituents and efficacy in human subjects is needed to confirm its potency as a promising antidiabetic phytotherapy.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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