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# THE ANTI-DIABETIC EFFECT OF *PHYLLANTHUS EMBLICA* ON RODENT MODELS: A SCOPING REVIEW AND META ANALYSIS

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**Abstract**

There are growing studies in the field of managing diabetes by using the natural remedies which demonstrate the efficacy of herbal plants in lowering down the blood glucose level. The use of natural remedies in diabetes management is still crucial since they offer a wider range of therapeutic benefits which renders great opportunity in providing a potential alternative approach that can increase the effectiveness in managing diabetes. The medicinal plants contain various kind of biologically active compounds with potential synergistic effects such as *Phyllanthus emblica* have antioxidant and anti-inflammatory effects that are oriented at multiple pathways that contribute to the antidiabetic action. Additionally, natural remedies can also accommodate the preferences of patients, cultural norms, and individualised treatment plans. Therefore, this research aimed to gather the existing evidences to comprehensively evaluate the therapeutic potential of *Phyllanthus emblica* in managing diabetes in the rodent models and determine the overall effect size of the *Phyllanthus emblica* on the key diabetes-related parameters such as blood glucose level, HbA1c and blood insulin level. A thorough search on databases PubMed, Mendeley, Web of Science, Scopus and Cochrane Library without date restriction were performed based on the PRISMA guidelines. Subgroup analyses was performed based on the gender, PE parts, rodents' types and diabetes induction method for each diabetes-related parameter. The pooled effect size obtained from meta-analysis of effects of PE extracts on the blood glucose level is -3.19 [-4.88, -1.50], $p = 0.0002$, $I^2 = 87\%$, on HbA1c is -4.42 [-7.00, -1.83], $p = 0.0008$, $I^2 = 80\%$, while for blood insulin level is 3.46

[1.62, 5.30], $I^2$ = 81%, p = 0.0002. The overall pooled effect results revealed the ability of PE extracts in reducing the blood glucose level, HbA1c and improving the blood insulin level in the diabetic rodent models. The is no significant difference between males and females (p = 0.62), PE parts (fruits or leaves) and stembarks (p = 0.72) or the types of rodents (p = 0.16) on the effect of PE extracts on the blood glucose levels. In contrast, there are statistically significant differences between the males and females (p = 0.007), PE parts (fruits or leaves) (p = 0.007) or the types of rodents (p = 0.007) effect of PE extracts on the HbA1c in rodents' models while the diabetes induction method (p = 0.90) does not have any significant difference. In view of the effects of PE extracts on the blood insulin level, there is statistically significance in diabetes induction method (p = <0.0001) while there is no statistically significance on effects of PE extracts on the blood insulin level between the males and females (p = 0.30), fruits and leaves (p = 0.90), or rats and mice (p = 0.07).

**Keyword:** *Phyllanthus emblica*, glucose, diabetes, rodent models

## Introduction

Diabetes mellitus is classified into type I diabetes and type II diabetes which characterized by a rise in blood glucose level above the normal blood glucose level. Type II diabetes is a condition in which the body does not respond to insulin's effects or there is insufficient production of insulin in the body. Whereas, type I diabetes patient are insulin dependent as their body does not produce insulin or there is little insulin production (World Health Organization, 2023). In addition, diabetic patients usually have diabetes associated with complications such as dyslipidaemia and hypertension which can further worsen the condition to cause development of cardiovascular diseases.

According to the global findings of International Diabetes Federation (2021), there is a growing trend in the diabetes prevalence where 537 million adults from the age group of 20 to 79 years old in year 2021 are diabetic patients and it is estimated to increase remarkably by 16.5% (643 million) in 2030 following by a surge of 17.9% (783 million) in 2045. Among the total of 537 million diabetic patients, 90 million of them are from South East Asia which is the second highest to the Western Pacific at 206 million people living with diabetes. Hence, the needs of continually in search of alternatives for diabetes prevention and treatment is essential.

The present treatments available for diabetes includes the most common use of oral or injectable Metformin (biguanides), and the others are oral Dipeptidyl Peptidase IV (DPP-4) Inhibitors, oral or injectable Glucagon-like Peptide-I Receptor (GLP-1) Agonists, oral Sodium-Glucose Cotransporter-II Inhibitors, insulin secretagogues, and oral thiazolidinediones (Endocrine Society, 2023). Apart from that, there are growing studies in the field of managing diabetes by using the natural remedies which demonstrate the efficacy of herbal plants in lowering down the blood glucose level. The use of natural remedies in diabetes management is still crucial since they offer a wider range of therapeutic benefits which renders great opportunity in providing a potential alternative approach that can increase the effectiveness in managing diabetes. The medicinal plants contain a variety of biologically active compounds with potential synergistic effects. These compounds also have antioxidant and anti-inflammatory effects that are oriented at multiple pathways that contribute to the antidiabetic action such as *Phyllanthus emblica* possess these two properties as well. Additionally, natural remedies can also accommodate the preferences of patients, cultural norms, and individualised treatment plans.

*Phyllanthus emblica Linn.* known as *Indian gooseberry*, *Emblica Officinalis Gaertn.* or *Amla* is the member of Euphorbiacea family. The fruit of *Phyllanthus emblica* is nourishing in vitamin C, amino acid and minerals, alkaloids, gallotanins, ellagic acid, corilagin, ellagitannins, gallic acid, emblicanin A and B, flavonoids such as rutin and quercetin as well as other biological components which makes it a valuable medicinal plant (Ahmad *et al*., 2021; D'Souza J *et al*., 2014; S. Mirunalini *et al*., 2010). There are cumulative studies suggested the potential beneficial therapeutic effects of *Phyllanthus emblica* as antiulcerogenic, neuroprotection, anti-diabetic, hypolipidemia, anti-oxidant, anti-microbial, anti-inflammatory and anticarcinogenic agent (Li *et al*., 2020; Liu *et al*., 2009; Liu *et al*., 2012; Saini *et al*., 2022; Srinivasan *et al*., 2018; Xu *et al*., 2016). Numerous studies have investigated the potential therapeutic effects of *Phyllanthus emblica* extract on rodent models. However, the existing evidence remains scattered and inconclusive. Furthermore, from our initial searching, there was limited to none existence of scoping review and meta-analysis reporting on the anti-diabetic effect of *Phyllanthus emblica* on rodent model. By synthesizing the available data, this present study intends to provide a comprehensive assessment of the efficacy of *Phyllanthus emblica* and highlight potential avenues for further research.

## Methodology

### *Search Strategy*

The scoping review and meta-analysis were conducted using the evidenced-based Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The flow chart of the search strategy is shown in figure 1. The methodology involved a comprehensive search on electronic databases, including PubMed, Mendeley, Web of Science, Scopus and the Cochrane Library to identify all the latest relevant studies that have investigated the anti-diabetic effects of PE on the rodent models. The literatures were screened by two independent reviewers to determine the eligibility for inclusion according to the inclusion criteria, title, abstracts, publication type and duplication. Then, full-text articles that meet the inclusion criteria were retrieved for further assessment in which the remaining articles after full-text assessment were included in the scoping review. Any discrepancies were resolved through consensus or consultation with a third reviewer. The search strategy included the keywords related to "*Phyllanthus emblica*", "*Amla*", "*Indian gooseberry*", "rodent models", "in vivo", "animals", "diabetes", "diabetes mellitus", "type-1 diabetes", "type-2 diabetes",

"insulin", and "anti-diabetic effect." The search strategy was limited to studies published in English and no date restriction. Additionally, the reference lists of retrieved journal articles imported to the EndNote were manually checked to ensure there were no duplicated articles had been missed despite remove duplication by filter was performed.

*Eligibility Inclusion Criteria for Study Selection*

The main criteria that need to be satisfied by the studies identified to be deemed as relevant and eligible are as the following: a) primary research, b) in vivo animal or rodent study, c) published in English language d) PICO (Population-rodent models, Intervention- treatment with *Phyllanthus Emblica* extract, Control- control group that are not treated with *Phyllanthus Emblica* extract, Outcomes- diabetes related parameters such as blood glucose level, insulin level, and HbA1c). Conversely, studies that performed by in-vitro method, or in human subjects, review articles, editorials, letter to editors and abstracts without the full details required were excluded during articles screening. This scoping review focused on all latest available literature related to the therapeutic effects of PE in treating or managing diabetes in rodent models by in-vivo study to provide a comprehensive evaluation of its anti-diabetic effects which can serve as a foundation for future research in this field.

*Data Extraction*

The following information were extracted from the eligible studies: author, publication year, study design, species, gender of the rodent models used, sample size, diabetes induction method, intervention, administration route, outcome measures, and results.

*Meta Analysis & Subgroup Analyses*

A meta-analysis was performed using a random-effect model to calculate the overall effect size of PE on rodent models. The effect size was expressed as the standardized mean difference and its 95% confidence interval (CI). Heterogeneity was assessed using the I-squared ($I^2$) statistics with p-value which give a ballpark figure for the percentage of the variance in study results that is attributable to the actual variations rather than the random variation. High $I^2$ of > 50% indicates that there is high heterogeneity across the outcomes of the studies and so randomized effect models should be used in meta-analysis. Whereas, $I^2$ of ≤ 50% indicates the outcomes across the studies are homogenous (Julian P. T. Higgins *et al*., 2002). Subgroup analyses was performed to explore the sources of heterogeneity and to identify any factors that may have influenced the effect size.

*Results Reporting*

The results of this scoping review and meta-analysis were reported according to the PRISMA guidelines. The results included a summary of the study selection process, the risk of bias assessment, and the results of the meta-analysis, including the effect size, heterogeneity, and subgroup analysis. The methodology designed is to ensure that the results are robust and that the sources of heterogeneity are identified and explored.

*Statistical Analysis*

Statistical analysis and meta-analysis were carried out using Cochrane RevMan. Results will be considered as statistically significant with the $p < 0.05$.

## Results

*Search Results*

A thorough search on the databases of PubMed (17), Mendeley (14), Scopus (15) and Web of Science (5) resulted in a total of 51 articles. Removal of duplicates, reviews, and those that are not met the inclusion criteria was performed which accounts 33 articles in total. After removal, the 18 remaining articles were subjected to full-text assessment. 12 articles were subjected to scoping review upon removal of 6 articles in full-text assessment. However, 3 articles out of the 12 articles were not managed to obtain the full-text, therefore, only 9 articles were included in total. The search string used were tabulated in Table 1 and flow diagram of literature search was as shown in Figure 1.

Table 1 Search strategy used for each database

| No. | Database | Search strategy | Total results (n= 51) Number of results retrieved |
|---|---|---|---|
| 1 | PubMed | All field ((((('Phyllanthus emblica') OR ('Amla')) OR ('Indian gooseberry')) AND (International Diabetes Federation, #2)) NOT ('in vitro'[Title/Abstract])<br>Limits: other animals, English | 17 |
| 2 | Mendeley | 'Phyllanthus emblica' OR 'Amla' OR 'Indian gooseberry' AND diabet*<br>Limit: Journal for document type | 14 |
| 3 | Scopus | Article title, Abstract, Keywords "Phyllanthus emblica" OR "amla" OR "Indian gooseberry"AND diabet* AND NOT "in vivo" AND NOT "human" AND "glucose"<br>Limit: English, exclude review (25), book chapter (3), short survey (2), editorial (2), note (1), conference review (1), conference paper (2)<br>Keyword filter:<br>• limited to Phyllanthus Emblica, article, nonhuman, animal model, antidiabetic activity, controlled study, antidiabetic agent, hypoglycaemic agents<br>• excluded antimicrobial activity, antineoplastic activity, in vitro study, major clinical study, high performance liquid chromatography, medicinal plant, oxidative stress, B-glucogallin, herb-drug interaction, triacyglycerol, Terminalia, Terminalia Chebula, Terminalia Bellirica, Aegle Marmelos, lipid profile, cholesterol, Clerodendrum, Ethnobotanical survey, Pterocarpus Marsupium, Ocimum Tenuiflorum, Ocimum, Mus, Melastoma Malabathricum, liver protection, lipid peroxidation, Leucas Aspera, lipid metabolism, hyperlipidemia, high density lipoprotein cholesterol, flow kinetics, Eupatorium, Erythrina Variegata, Eclipta Prostrata, Elipta, Dryopteris Filixmas, Dryopteris, Drug synthesis, Drug Screening, Dillenia Indica, Cuscuta Reflexa, Cuscuta, Curcumin, Computer Model, Curcuma Longa Extract, Commiphora, Coccinia Grandis, Clitoria, Clitoria Ternatea, Cinnamomum Zeylanicum, Cinnamomum Zeylanicum Extract, Centella Asiatica, Bulk Density, Ananas Comosus, Achyranthes Aspera, Achyranthes, Abutilon Indicum | 15 |
| 4 | Web of Science | Phyllanthus emblica AND diabet* NOT "in silico" NOT "patient" NOT "in vitro" (Title)<br>Limit: exclude review, English | 5 |
| 5 | Cochrane Library | ------ | 0 |

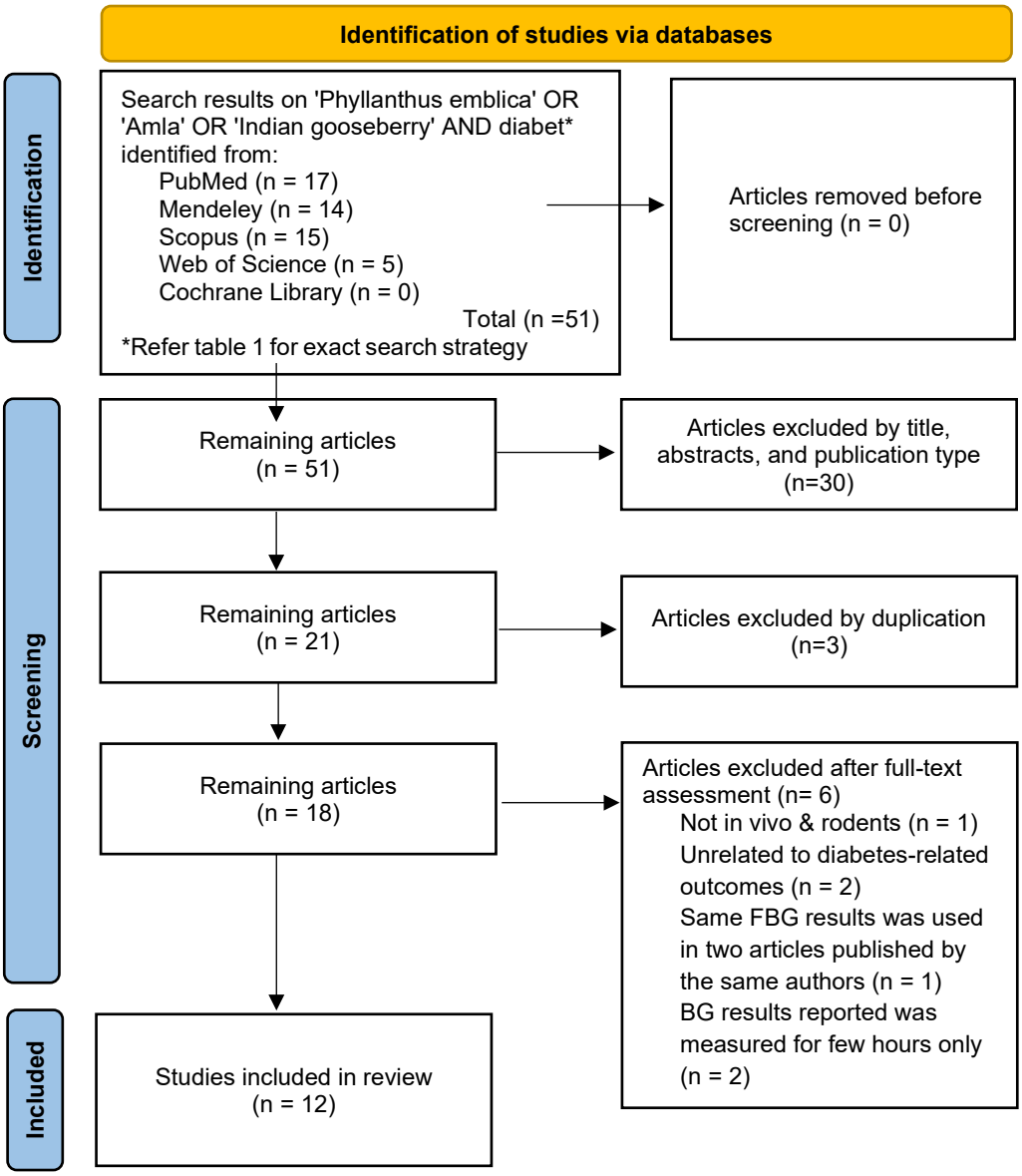


Fig. 1 Flow diagram of literature search

*Antidiabetic rodent studies of P. embilica*

The detailed main aspects of each study were shown in the following Table 2. The sample size of each study ranging from 3 to 12. Among the 9 included studies, rodents were treated with the extracts from fruits in 6 studies, leaves in 1 study, stembarks in 1 study and 1 study did not specify extracts was isolated from which part of the *PE.* The diabetes induction method by chemical is including Streptozotocin (STZ) in 6 studies, Cyclophosphamide in 1 study, and Arsenic in 1 study. One included study was carried out the study in two different group of mice which are Cyclophosphamide-accelerated non-obese diabetic model (Cyp-NOD) and Spontaneous non-obese diabetic model (S-NOD). Male rodents were used in 6 studies, female rodents in 1 study while either sex of the rodents in 1 study and gender was not specified in 1 study. Blood glucose levels were reported in 8 studies with 3 of them did not report the initial baseline blood glucose level and for S-NOD mice in 1 study. HbA1c were reported in 3 studies, plasma or serum insulin level in 5 studies with 3 of them did not report the initial baseline of the insulin level. As such, the meta-analysis on effects of the PE on the blood glucose levels, HbA1c and blood insulin levels were comparing their values after PE extracts treatment with the diabetic control groups that are not treated with the extracts. Table 3 presents the results of diabetes-related outcomes from the included studies, which were utilized for further meta-analysis.

Table 2 Study characteristics of the included articles

| Authors (Year) | Parts of PE | Species | Rodent models, Diabetes Induction method | Sex | Age or weight at the baseline | n (Tx/no tx) | Dose (mg/kg BW) | Duration exposed to PE | Route of Administration | Diet | Blood sample for BG | HbA1c (%) | Measurements |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Al-Twaty et al. (2014) | Fruits | Albino | Adult rats, STZ 50 mg/kg dissolved in citrate buffer (0.01 M, pH 4.5) | male | 100-120 g | 10/10 | 25 mg/kg/day of PE Nanoparticles, 50 mg/kg/day of PE Nanoparticles, 100 mg/kg/day of PE Nanoparticles | 30 days | Oral | standard laboratory diet (protein, 16.04%; fat, 3.63%; fiber, 4.1%; and metabolic energy, 0.012 MJ), water ad libitum | Serum | NA | Serum glucose level |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ansari et al. (2014) | Fruits | Long Evans | Adult rats, STZ 90 mg/kg BW in 10mL citrate buffer | male | Approx.180-220 g | 8/8 | 1.25g/10mL/ kg BW of E.O aqueous extracts | 8 weeks | Oral | standard laboratory pellet diet, water ad libitum | Serum | NA | FSG, serum insulin level |
| Lin et al. (2023) | Fruits | NOD/ShiLtJ mice | Mice, 200 mg/kg body weight by IP twice 14 days for cyclophosphamide - accelerated diabetes | female | 3weeks (S-NOD mice), 4 weeks old (Cyp-NOD mice) | 7/7 (S-NOD mice), 12/12 (Cyp-NOD mice) | 400 mg/kg BW once daily EA of PE extracts | 15 weeks (S-NOD), 4 weeks (Cyp-NOD) | Oral | NS | NS | Refer to table 3 | BG, insulin levels, HbA1c |
| Mohanty et al. (2021) | Fresh fruits | Wistar rats | Rats, STZ 45 mg/kg BW | NS | 150–200 g | 7/9 standardized hydro-alcoholic PE fruit extracts | 300 mg/kg BW | 4 weeks | Orally | NS | NS | 8.65±1.8 (Montomoli, #15), 10.4±2.3 (STZ control) | HbA1c |
| Nain et al. (2012) | Leaves | Albino Wistar rats | Rats, STZ 50 mg/kg | male | 7–8 weeks, | 6/6 | hydro methanolic EO extract | 45 days | Oral | Pellet, water ad libitum | Serum | Refer to table 3 for more details | FBG, plasma insulin level, HbA1c |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | BW in 0.1 M citrate buffer (pH 4.5) | | 200–250 g | | 100mg/kg, 200mg/kg, 300mg/kg, 400mg/kg BW | | | | | | |
| Quranay ati et al. (2023) | Stem barks | Rattus norvegic us | Rats, STZ 30 mg/kg BW in suspensi on of CMC 0.5% | male | 2-3 months, 200-300g | 3/3 (n-hexane, ethyl acetate, methan ol extracts of PE stem barks) | 200 mg/kg BW of extracts suspended in CMC 1% | 4 weeks | Orally & assisted by nasogas tric tube then fed with standar dized comme rcial feed during interve ntion period | High fat diet (5% cheese, 10% egg yolk, 15% cow's fat, 5% vegetable oil, 45% rice, and 20% commerc ial feed) | NS | NA | FBG |
| Singh et al. (2020) | Fruits | Balb/c mice | Mice, diabetes induction method using arsenic along with treatment | male | 23 ± 2 g | 8/8 | 500 mg/kg BW of PE fruit extract suspended in 2% gum acacia | 30days | Oral with canula | pellet diet, filtered water ad libitum | Serum | NA | FBG, fasting serum insulin levels |
| Tirgar et al. (2010) | Fruits | Wistar rats | Rats, STZ 45 mg/kg | Either sex | 150-200 g | 6/6 | 5 ml/kg/day E.O fruits | 4 weeks | Oral | conventi onal laborator | Serum | NA | Serum glucose, serum insulin levels |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | dissolved in 0.9 % NaCl | | | | fresh juice, 100 mg/kg/day E.O hydro alcoholic extract | | | y diet, tap water ad libitum | | | |
| Tiwari et al. (2011) | NS | Wistar rats | Rats, 45 mg/kg streptozotocin in citrate buffer (pH 4.4, 0.1 M) by IP | male | 220–260 g | 5-8/ 5-8 | 250, 500 and 1000 mg/kg/day of PE aqueous extracts | 4 weeks | Oral gavage | NS | Plasma | NA | PBG |

STZ: Streptozotocin, NS: not specified, NA: not available, FBG: fasting blood glucose, Tx/no-tx: treatment/not treatment with PE extracts, HFD: high fats diet, BW: body weight, PE: *Phyllanthus emblica*, HbA1c: Glycated haemoglobin, STZ control = diabetic control, S-NOD: spontaneous non-obese diabetes, Cyp-NOD: cyclophosphamide-accelerated non-obese diabetes, EA: ethyl acetate, IP: intraperitoneal, PBG: plasma blood glucose, EO: Emblica Officinalis, FSG: fasting serum glucose

Table 3 Results of diabetes-related outcomes for included studies

| Authors (Year) | Sample size | | BG (mmol/L) | | | Results reported in | HbA1c (%) | Plasma insulin (ng/dL) | |
|---|---|---|---|---|---|---|---|---|---|
| | DM control | DM + PE | | Initial | After | | | Initial | After |
| Al-Twaty and Booles (2014) | 10 | 10 | Diabetic control | #20.49±1.06 | #21.40±1.25 | Mean±SEM | NA | NA | |
| | | | DM+PE 25mg/kg/day | #20.24±1.18 | #7.35±0.59 | | | | |
| | | | DM+PE 50mg/kg/day | #20.24±1.13 | #6.25± 0.62 | | | | |
| | | | DM+PE 100mg/kg/day | #20.32±1.24 | #4.87± 0.51 | | | | |
| Ansari et al. (2014) | *8 | *8 | Type 2 WC | 10.01±1.27 | 6.29±1.19 | Mean±SD | NA | 0.51±0.21 | 0.24±0.13 |
| | | | Type 2 AE | 10.23±1.36 | 6.75±0.50 | | | 0.48± 0.26 | 0.38±0.17 |
| ¶ Lin et al. (2023) | 7 (S-NOD mice), 12 (Cyp-NOD) | 7 (S-NOD mice), 12 (Cyp-NOD) | S-NOD mice | Control | #8.99±0.31 | Mean±SEM | 7.26±0.18 | Not reported | @@55±0.8 |
| | | | | EA of PE extracts | #6.22±0.00 | | 5.34±0.10 | | @@ 116±1 |
| | | | Cyp-NOD mice | Control | #8.85± 0.16 | | 7.74±0.09 | | @@ 64±4 |
| | | | | EA of PE extracts | #7.25± 0.29 | | 5.74±0.08 | | @@ 111±1 |
| | | | STZ-control | Not reported | #3.91±0.08 | | 10.4 ± 2.30 | Not reported | |
| | | | | | #4.16± 0.14 | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mohanty et al. (2021) | 9 | 7 | Standardized hydro-alcoholic PE extract | NA | | Not stated | 8.65 ± 1.80 | NA |
| Nain et al. (2012) | 6 | 6 | Diabetic control | #16.57±0.12 | #18.88±0.40 | Mean±SEM | 14.45±1.10 | ##21.15±2.71 ##12.96±2.54 |
| | | | E.O extract 100mg/kg BW | #15.71±0.21 | #11.22±0.31 | | 12.70±0.90 | ##22.05±3.31 ##27.63±2.82 |
| | | | E.O extract 200mg/kg BW | #16.12±0.17 | #9.08±0.22 | | 11.15±0.90 | ##24.60±4.00 ##31.50±5.95 |
| | | | E.O extract 300mg/kg BW | #15.96±0.16 | #7.62±0.17 | | 9.70±0.83 | ##26.20±3.90 ##41.05±4.53 |
| | | | E.O extract 400mg/kg BW | #15.49±0.14 | #5.74±0.18 | | 8.34±0.89 | ##23.94±4.07 ##44.91±3.83 |
| Quranayati et al. (2023) | 3 | 3 | STZ-control | #28.28±6.93 | #10.82 ± 1.10 | Mean±SD | NA | NA |
| | | | n-Hexane extract of PE | #23.04± 3.21 | #10.10 ± 2.45 | | | |
| | | | Ethyl acetate extract of PE | #27.36±4.20 | #6.31 ± 0.83 | | | |
| | | | Methanol extract of PE | #24.82±7.51 | #10.41 ± 1.09 | | | |
| ¶ Singh et al. (2020) | **8 | **8 | DM Control | | | | | |
| | | | (ARS treated) | | # 8.63±0.41 | | NA | Not reported @ 27.8±0.9 |
| | | | ARS+E.O fruit extracts 500mg/kg treated | Not reported | # 6.17±0.36 | Mean±SEM | | @ 43.5±2.9 |
| Tirgar et al. (2010) | 6 | 6 | Diabetic control | | #21.76±0.91 | Mean±SEM | | ##42.96±4.63 |
| | | | Diabetic+ E.O fresh fruit juice | | #8.17±0.58 | | NA | Not reported ##64.81±3.20 |
| | | | Diabetic+ E.O hydroalcoholic extract | Not reported | #5.89±0.25 | | | ##62.13±5.64 |
| Tiwari et al. (2011) | 5-8 | 5-8 | STZ control | | #26.03±0.65 | | | |
| | | | STZ+E.O (250) | Not reported | #19.19±0.33 | Mean±SEM | NA | NA |
| | | | STZ+E.O (500) | | #13.40±0.63 | | | |

| | | |
|---|---|---|
| | STZ+E.O (1000) | [#]8.11±0.34 |

HbA1c = glycated haemoglobin (%), STZ control = diabetic control, BG = blood glucose, S-NOD: Spontaneous non obese diabetes, Cyp- NOD: cyclophosphamide-accelerated non obese diabetes, EA: ethyl acetate, E.O: Emblica officinalis aqueous extract, AE: aqueous extracts, Type 2 WC: Type 2 water control = non-insulin dependent diabetes mellitus control group fed with deionized water, DM: diabetes mellitus, ARS: Arsenic

¶ Data are extracted from chart using online converter

*8 rats were assigned randomly to each group, however, results on serum insulin level for Type 2 WC (n=5) and Type 2 AE (n=6) were reported.

**8 rats were randomly divided into each group, however, results reported on fasting blood glucose and serum insulin level are mean ± SEM of 5 animals in each group only.

[@]unit of serum insulin level converted from ng/mL to ng/dL using online converter

[@@]unit converted from µg/L to ng/dL

[#] unit converted from mg/dL to mmol/l using online converter

[##]unit converted from µU/mL to pmol/L using conversion factor of 6 and multiplied with the molar mass of insulin (5808) and converted to ng/dL

*Forest plot Analysis on effects of PE extracts on blood glucose levels in DM rodents*

Eleven studies from 7 articles enrolling 69 diabetic control rodents and those treated with PE extracts respectively with reported blood glucose levels were included in meta-analysis except 1 article with reported blood glucose levels was excluded from meta-analysis due to the sample size of rodents used was reported in range which does not have an exact quantity. Six studies showed the PE extracts treatment reduced the blood glucose levels in the diabetic rodent models; four studies did not show any statistically significant effects. 1 study was not estimable due to the standard deviation was not able to be extracted from the line chart reported by the author as the standard deviation value is too small. By combining all these studies in meta-analysis using random-effects model and standardized mean difference, the results revealed the PE extracts reduced the blood glucose levels of diabetic rodents with 95% confidence interval at -3.19 [-4.88, -1.50], p = 0.0002 (<0.05 statistically significant), $I^2$ = 87%. There is high heterogeneity across the outcomes of the studies as the $I^2$ >50% and the p-value for heterogeneity is <0.00001 which indicates the hypothesis of no heterogeneity is rejected (Figure 2).

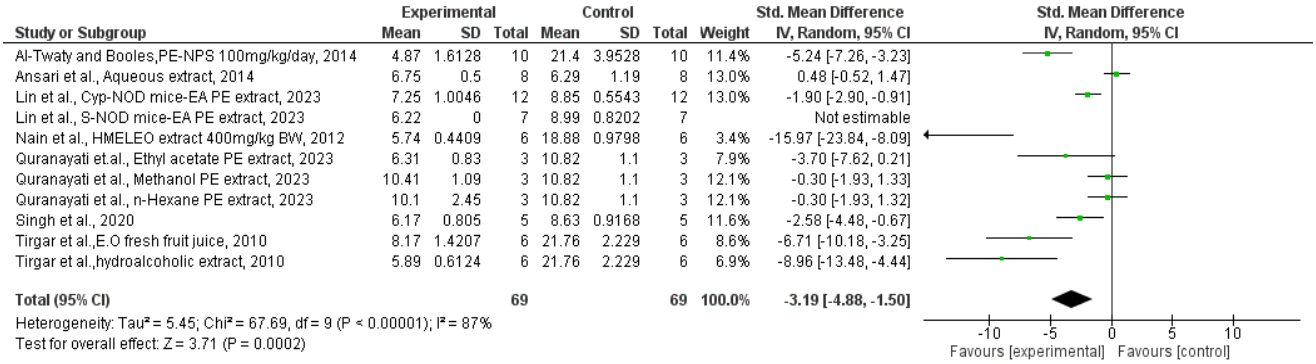


Fig. 2 Forest plot of effects of PE extracts on blood glucose levels in DM rodents

*Forest plot Analysis on effects of PE extracts on HbA1C in DM rodents*

Three studies from 2 articles enrolling a total of 25 diabetic control rodents and those treated with PE extracts respectively were included in the meta-analysis. All three studies shown the antidiabetic activity of the PE extracts on the HbA1c of the diabetic rodents treated groups. Pooling of all three studies in meta-analysis using random-effects model and standardized mean difference, the results demonstrate PE extracts able to reduce the HbA1c in diabetic rodents with 95% confidence intervals -4.42 [-7.00, -1.83], p = 0.0008 (statistically significant). There is high heterogeneity across the outcomes of the studies as the $I^2$ = 80%

which is >50% and the p-value of heterogeneity = 0.007 indicates the hypothesis of no heterogeneity is rejected. One study with reported HbA1c was excluded from meta-analysis because the results reported were not mentioned they are reported in SEM or SD.

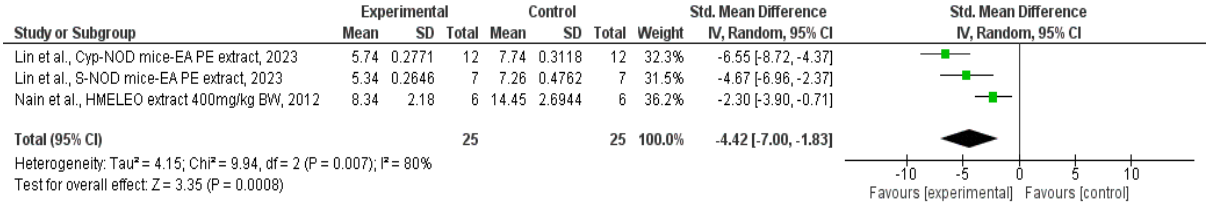


Fig. 3 Forest plot of effects of PE extracts on HbA1c in DM rodents

*Forest plot Analysis on effects of PE extracts on blood insulin level in DM rodents*

Six studies from 4 articles with reported blood insulin levels were included in the meta-analysis. 1 study was excluded from meta-analysis due to the serum insulin levels reported in ng/dL were very small figures which are huge differences compared to the reported insulin levels in other studies of the same measurement unit in ng/dL. By pooling all six studies in meta-analysis using random-effects model and standardized mean difference, it shows an increment of the blood insulin levels in the PE extracts treated groups compared to the diabetic control groups with 95% CI 3.46 [1.62, 5.30], p = 0.0002 (statistically significant), $I^2$ = 81%. The p-value of heterogeneity = 0.0001 indicates the hypothesis of no heterogeneity is rejected.

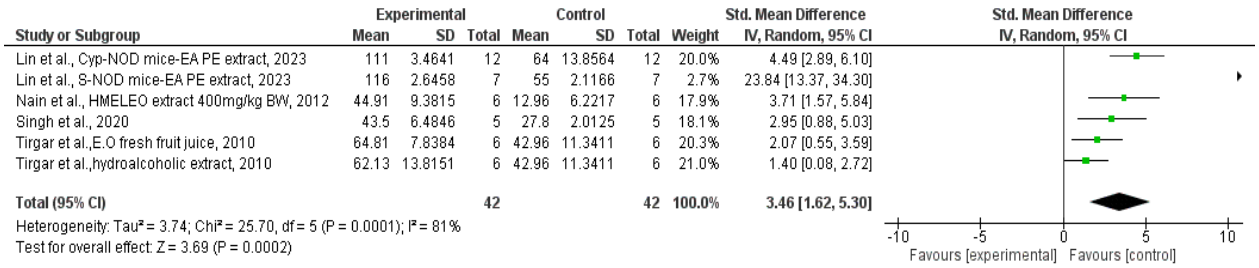


Fig. 4 Forest plot of effects of PE *e*xtracts on blood insulin level of DM rodents

*Subgroup Analysis on effects of PE extracts on blood glucose levels in DM rodents*

Subgroup analyses by the rodents' gender, parts of PE, types of rodents, and diabetes induction method were performed to explore the sources of heterogeneity and to identify any factors that may have influenced the effect size on blood glucose levels. The heterogeneity presented in the 9 studies of gender subgroup (p< 0.00001, $I^2$ = 85%), hence, random-effect

model was used in the meta-analysis giving a result of -2.23[-3.84, -0.61], Z = 2.70 (p = 0.007) at 95% CI. Furthermore, the heterogeneity presented in 11 studies of PE parts, rodents' types, and diabetes induction method respectively are the same (p< 0.00001, $I^2$ = 87%), as such, random-effect model was used and the pooled mean result was -3.19 [-4.88, -1.50], Z = 3.71(p = 0.0002). The results of pooled mean analysis showed the hypoglycaemic activity of the PE extracts.

| Subgroups | No. of studies | Effect size 95% CI | | p-value | Heterogeneity ($I^2$) | Test for subgroup difference (p-value) |
|---|---|---|---|---|---|---|
| **Gender** | | | | | | |
| Male | 7 | -4.53 | -0.43 | 0.02 | 87% | 0.62 |
| Female | 2 | -2.90 | -0.91 | 0.0002 | Not applicable | |
| **PE parts** | | | | | | |
| Fruits | 7 | -5.8 | -1.37 | 0.002 | 90% | 0.72 |
| Leaves and stembarks | 4 | -6.06 | 0.34 | 0.08 | 82% | |
| **Rodent types** | | | | | | |
| Rats | 8 | -6.29 | -1.47 | 0.002 | 89% | 0.16 |
| Mice | 3 | -2.93 | -1.17 | <0.00001 | 0% | |
| **Diabetes induction method** | | | | | | |
| Chemical | 10 | -4.88 | -1.5 | 0.0002 | 87% | not applicable |
| Spontaneous | 1 | not estimable | | not applicable | not applicable | |

Table 4 Subgroup analysis of effects of PE extracts on blood glucose levels in DM rodents

The effect of PE extracts on the blood glucose levels may not have significant difference between the males and females (p = 0.62), PE parts either fruits or leaves and stembarks (p = 0.72) or the types of rodents (p = 0.16). The 95% CI, p-value, $I^2$ and p-value of test for subgroup difference for the study involving the spontaneous non-obese diabetic mice are inestimable due to the standard deviation was unable to be extracted from the line chart reported by the author as the standard deviation value is too small. The p-value of each aspect under each subgroup are <0.05 which confirms the effect size does not cross the line of no-effect except for leaves and stembarks in PE parts subgroup (p = 0.08, not statistically significant) and spontaneous non-obese diabetic mice under diabetes induction method that is inestimable. There is no heterogeneity present in the three studies that enrolled the mice models

($I^2$ = 0%, p <0.00001). The results revealed the ability of PE extracts in reducing the blood glucose levels in the PE extracts treated group compared to the diabetic control group.

*Subgroup Analysis on effects of PE extracts on HbA1c in DM rodents*

Subgroup analyses by the rodents' gender, PE parts, types of rodents, and diabetes induction method were explored to identify the sources of heterogeneity and any factors that may have influenced the effect size on HbA1c in the diabetic rodents. The presented heterogeneity is the same in all subgroups which are p = 0.007, $I^2$ = 80% at 95% CI, hence, random-effect model was used in the pooled analysis resulting in -4.42 [-7.00, -1.83], Z = 3.35 (p = 0.0008). The pooled mean revealed the reduction of HbA1c in the PE extracts treated groups in comparison to that in the diabetic control untreated groups.

There are statistically significant differences between the males and females (p = 0.007), PE parts either fruits or leaves (p = 0.007) or the types of rodents (p = 0.007) effect of PE extracts on the HbA1c in the rodents' models while the diabetes induction method (p = 0.90) does not have any significant difference. The heterogeneity within the subgroup of male, leaves and stembarks, rats or spontaneous-non obese diabetic mice were not able to be detected due to the reason of only one single study is available in them, hence, no comparison can be made and detected. The p-value for each aspect under the subgroups of gender, PE parts, rodents' types, and diabetes induction method are <0.05 which confirms the effect size are statistically significant and they do not cross the line of no-effect. In short, the results shown that the PE extracts have favourable effects on HbA1c where it reduced the HbA1c in the PE extracts treated groups compared to the diabetic control groups.

Table 5 Subgroup Analysis on effects of PE extracts on HbA1c in DM rodents

| **Subgroups** | **No. of studies** | **Effect size** | | **p-value** | **Heterogeneity ($I^2$)** | **Test for subgroup difference (p-value)** |
|---|---|---|---|---|---|---|
| | | **95% CI** | | | | |
| **Gender** | | | | | | |
| Male | 1 | -3.90 | -0.71 | 0.005 | Not applicable | 0.007 |
| Female | 2 | -7.48 | -3.80 | <0.00001 | 26% | |
| **PE parts** | | | | | | |
| Fruits | 2 | -7.48 | -3.80 | <0.00001 | 26% | 0.007 |
| Leaves | 1 | -3.90 | -0.71 | 0.005 | Not applicable | |
| **Rodent types** | | | | | | |
| Rats | 1 | -3.90 | -0.71 | 0.005 | Not applicable | 0.007 |
| Mice | 2 | -7.48 | -3.80 | <0.00001 | 26% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Diabetes Induction method** | | | | | | |
| Chemical | 2 | -8.51 | -0.20 | 0.04 | 89% | 0.90 |
| Spontaneous | 1 | -6.96 | -2.37 | <0.0001 | not applicable | |

*Subgroup Analysis on effects of PE extracts on blood insulin levels in DM rodents*

A subgroup analysis was performed based on the gender, PE parts, types of rodents, and diabetes induction method. For subgroup of gender, there is existence of heterogeneity in the total of 4 studies ($p = 0.002$, $I^2 = 80\%$), hence, random-effect model was employed in the pooled analysis resulting in 95% CI at 4.97 [2.13, 7.82], $Z = 3.42$ ($p = 0.0006$). On the other hand, the existed heterogeneity in total of 6 studies ($p = 0.0001$, $I^2 = 81\%$) are the same for subgroups of PE parts, rodent types and diabetes induction method respectively which showed the pooled mean of 3.46 [1.62, 5.30], $Z = 3.69$ ($p = 0.0002$) at 95% CI. All these pooled analyses revealed that PE extracts treated groups have higher blood insulin levels than that in the diabetic control groups.

| **Subgroups** | **No. of studies** | **Effect size 95% CI** | | **p-value** | **Heterogeneity ($I^2$)** | **Test for subgroup difference (p-value)** |
|---|---|---|---|---|---|---|
| **Gender** | | | | | | |
| Male | 2 | 1.83 | 4.81 | <0.0001 | 0% | 0.30 |
| Female | 2 | -5.46 | 32.35 | 0.16 | 92% | |
| **PE parts** | | | | | | |
| Fruits | 5 | 1.31 | 5.71 | 0.002 | 84% | 0.90 |
| Leaves | 1 | 1.57 | 5.84 | 0.0007 | Not applicable | |
| **Rodent types** | | | | | | |
| Rats | 3 | 0.98 | 3.35 | 0.0003 | 38% | 0.07 |
| Mice | 3 | 1.91 | 10.86 | 0.005 | 87% | |
| **Diabetes Induction method** | | | | | | |
| Chemical | 5 | 1.64 | 4.03 | <0.00001 | 60% | <0.0001 |
| Spontaneous | 1 | 13.37 | 34.3 | <0.00001 | not applicable | |

Table 6 Subgroup Analysis on effects of PE extracts on blood insulin levels in DM rodents

There is statistically significance in diabetes induction method ($p = <0.0001$) while there is no statistically significance on effects of PE extracts on the blood insulin level between the males and females ($p = 0.30$), fruits and leaves ($p = 0.90$), or rats and mice ($p = 0.07$). The heterogeneity within the subgroups of leaves or spontaneous-non obese diabetic mice were not detectable due to the reason of only one single study was included, hence, no comparison can

be made and detected within the subgroups. The p-value for each aspect under the subgroups of gender (male), PE parts, rodents' types, and diabetes induction method are <0.05 which confirms the effect size are statistically significant and they do not cross the line of no-effect except for female with p-value of 0.16 indicating the effect size crossed the line of no-effect, hence, it is not statistically significant. In sum, the results showed that the PE extracts increased the insulin level in blood of the PE extracts treated groups compared to the diabetic control groups.

**Discussion**

This study would be the first scoping review and meta-analysis that gathered the existing literatures to explore the antidiabetic activity of PE treatment on improvement of the blood insulin levels, reduction of the blood glucose levels and HbA1c in the diabetic rodent models. The pooled mean result of meta-analysis with 95% CI at -3.19 [-4.88, -1.50] on the effects of PE extracts on the blood glucose levels showed a reduction in blood glucose levels in treated groups compared to the control groups, however, if we look deeply in the forest plot, there are four studies crossed the line of no-effect, indicating the results of the four studies are statistically insignificant. This also suggest the variations across the outcomes of the studies included which was then confirmed by the result of heterogeneity, $I^2$ = 87% (p <0.00001). Moreover, all three studies in forest plot of the effects of PE extracts on the HbA1c are falls in the region of experimental side without crossing the line of no-effect which indicates the PE extracts treated groups have a lower HbA1c readings than that of the diabetic control groups with the pooled mean 95% CI at -4.42 [-7.00, -1.83], p = 0.0008. In contrast, all six studies in the forest plot analysis on effects of PE extracts on blood insulin level in DM rodents flavoured the control side due to the diabetic control groups have a lower blood insulin level which proved the ability of the PE extracts in enhancing the blood insulin level of the treated rodents' groups with 95% CI at 3.46 [1.62, 5.30], p = 0.0002. Overall, PE extracts possess the ability in lowering the blood glucose levels and HbA1c while increasing the blood insulin levels which would be useful as a complementary agent with other antidiabetic treatment instead of acting as a monotherapy alone.

The blood glucose levels and fasting insulin levels reported in the study conducted by Singh et al. (2020) were not included the initial baseline of both parameters in the control groups and treated groups. Hence, comparison between before PE extracts treatment and after the treatment in the treated groups cannot be detected. As such, the meta-analysis was conducted by comparing the results of the two parameters in the treated groups with the control

groups (not treated) respectively using random-effect model and standardized mean difference with 95% CI. In addition, the mice enrolled in the study were not diabetes induced in earlier but co-administration of the ARS with Amla to compare it with another group that was treated with ARS alone for the same duration of 30 days as the authors proved that ARS can induce diabetes in mice and co-administration of both ARS with Amla can reduce the blood glucose. However, as the diabetic rodents used was not induced diabetes earlier before initiation of the treatment, it would be unfair to compare with the other studies in the meta-analysis.

Another study carried out by Tirgar et al. (2010) enrolled either sex of the rats in the experiment, hence, it was excluded from the subgroup analysis for blood glucose levels, HbA1C and blood insulin levels. Besides that, in the forest plot analysis on effects of PE extracts on blood glucose levels in the DM rodents, it was observed that the estimated effect size of administrating the ethyl acetate extracts of PE in the STZ induced diabetic rats is -3.70 [-7.62, 0.21] compared to those treated with methanol extracts of PE (-0.30 [-1.93, 1.33]) and n-hexane extracts of PE (-0.30 [-1.93, 1.32]) in the study conducted by Quranayati et al. (2023). It can be seen that the ethyl acetate extracts of PE have significantly reduced the most in blood glucose levels of the diabetic rats as compared to another two types of PE extracts which is in line with the result reported by the authors of the study. Whereas, the estimated effects sizes of both methanol extracts of PE and n-hexane extracts of PE crossed the line of no-effect, indicates there is no statistically significant difference between the treatment groups and the control groups.

The overall pooled effects of all three studies in meta-analysis using random-effects model and standardized mean difference demonstrates the PE extracts declined the HbA1c in the PE extracts treated diabetic rodents with 95% confidence intervals -7.00 to -1.83, $p = 0.0008$ (statistically significant). This result may not be conclusive as it was based on the HbA1c results of the three included studies as there are only two articles included in the meta-analysis have reported HbA1c measurements. However, the results of the forest plot which flavours the experimental side indicates that PE extracts reduced the HbA1c in treated groups are in line with the results of HbA1c measurements reported by the authors of the two articles (Lin et al., 2023; Nain et al., 2012). This shown the potential of PE extracts in lowering the HbA1c.

## Conclusion

This comprehensive review and meta-analysis is a pioneering effort to comprehensively investigate the antidiabetic potential of PE extracts in rodent models of diabetes. A synthesis of the existing literature reveals excellent insights into the effects of PE extracts on key indicators of diabetes, including the blood glucose levels, HbA1c and blood insulin levels. A meta-analysis of the effect of PE extract on blood sugar levels showed a significant reduction in the treated groups compared to the control groups. However, closer examination of the forest plot results revealed four studies that crossed the line of no-effect, possibly indicating statistical significance between the treatment and control groups. These differences in results are supported by a high level of heterogeneity ($I^2$ = 87%, >50%), indicating that cautious interpretation is required.

In contrast, the impact of PE extracts on the HbA1c levels demonstrates a consistent and statistically significant reductions in treated groups compared to control groups. All three studies in this category show promising results in which reinforcing the potential of PE extracts in enhancing long-term glycaemic control.

In regards to the meta-analysis on blood insulin levels, the forest plot illustrates a favourable trend, with PE extracts enhancing insulin levels in treated rodent groups compared to diabetic control groups. This finding underscores the potential of PE extracts to ameliorate insulin resistance which is a crucial aspect in managing the diabetes.

Based on the findings, PE extracts have showed promising antidiabetic effects, particularly in lowering the blood glucose and HbA1c levels while enhancing the blood insulin levels. However, the heterogeneity observed and the presence of statistically insignificant results in some studies suggest the need of further study to elucidate the factors that may have contributed to these variations. Future studies should delve into the mechanisms behind the observed effects and explore any other potential factors that may have influence the outcomes. From the perspective of the clinical context, PE extracts may be can be used as complementary treatment or use in combination with other anti-diabetic regimens for the synergistic effects in diabetes management. Continuing research efforts are important for gaining a more comprehensive understanding of their mechanisms and effects.

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