© 2022 Journal of Pharmacy & Pharmacognosy Research, 10 (4), 737-747, 2022
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres22.1378_10.4.737

Review

The effect of *Aloe vera* on fasting blood glucose levels in pre-diabetes and type 2 diabetes mellitus: A systematic review and meta-analysis

[Efecto del *Aloe vera* sobre los niveles de glucosa en sangre en ayunas en prediabetes y diabetes mellitus tipo 2: Una revisión sistemática y meta-análisis]

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Abstract

Context: : *Aloe vera* is a traditional medicinal plant that shows a wide range of biological activities. Previous studies demonstrated the antihyperglycemic effect of *Aloe vera* but with inconsistent results.

Aims: To quantitatively summarize the effect of *Aloe vera* on fasting blood glucose in pre-diabetes and type 2 diabetes mellitus by a meta-analysis.

Methods: PubMed, Scopus, Springer Link, Science Direct, Proquest, and Google Scholar were used to identify clinical trials evaluating the effect of Aloe vera on fasting blood glucose published between 2011 and 2021. The inclusion criteria were: (1) original research with a clinical trial design evaluating the effect of *Aloe vera* on fasting blood glucose in pre-diabetes and/or type 2 diabetes mellitus; (2) providing the data of the mean fasting blood glucose and standard deviation in both control and intervention group, and; (3) *Aloe vera* was used as the only intervention. The pooled effect of *Aloe vera* on fasting blood glucose was evaluated using the random effect model, and publication bias was assessed by Funnel plots and Fail Safe-N.

Results: A total of 25 trials were included from 13 publications involving 642 patients. The results showed that *Aloe vera* significantly reduced fasting blood glucose (-0.35 [95% CI, -1454, -0.616] mg/dL; p<0.001) compared to control. *Aloe vera* might have a more remarkable effect in males, BMI not more than 30 mg/kg^2, type 2 diabetes mellitus, administered for ≥ 8 weeks, dose at 200 mg, and capsule administration. However, a high heterogeneity across the studies was found.

Conclusions: *Aloe vera* may reduce fasting blood glucose in pre-diabetes and type 2 diabetes mellitus. However, further study with a well-design and standardized preparation is needed to emphasize the effect of *Aloe vera* on blood glucose control.

Keywords: *Aloe vera*; hyperglycemia; meta-analysis; systematic reviews.

Resumen

Contexto: El *Aloe vera* es una planta medicinal tradicional que presenta una amplia gama de actividades biológicas. Estudios previos demostraron el efecto antihiperglucémico del *Aloe vera* pero con resultados inconsistentes.

Objetivos: Resumir cuantitativamente el efecto del *Aloe vera* sobre la glucemia en ayunas en prediabetes y diabetes mellitus tipo 2 mediante un meta-análisis.

Métodos: Se utilizaron PubMed, Scopus, Springer Link, Science Direct Proquest, y Google Scholar para identificar los ensayos clínicos que evaluaron el efecto del *Aloe vera* sobre la glucemia en ayunas publicados entre 2011 y 2021. Los criterios de inclusión fueron: (1) investigación original con un diseño de ensayo que evalúa el efecto del *Aloe vera* sobre la glucosa en sangre en ayunas en prediabetes y/o diabetes mellitus tipo 2; (2) proporcionar los datos de la media de glucosa en sangre en ayunas y la desviación estándar tanto en el grupo de control como en el de intervención, y; (3) Se utilizó *Aloe vera* como única intervención. El efecto combinado del *Aloe vera* sobre la glucosa en sangre en ayunas se evaluó mediante el modelo de efectos aleatorios, y el sesgo de publicación se evaluó mediante gráficos en embudo y Fail Safe-N.

Resultados: Se incluyeron un total de 25 ensayos de 13 publicaciones con 642 pacientes. Los resultados mostraron que el *Aloe vera* redujo significativamente la glucosa en sangre en ayunas (-0,35 [IC del 95 %, -1454, -0,616] mg/dL; p<0,001) en comparación con el control. El *Aloe vera* podría tener un efecto más notable en varones, IMC no superior a 30 mg/kg^2, diabetes mellitus tipo 2, administrado durante ≥ 8 semanas, dosis de 200 mg y administración en cápsula. Además, se encontró una alta heterogeneidad entre los estudios.

Conclusiones: El *Aloe vera* puede reducir la glucemia en ayunas en prediabetes y diabetes mellitus tipo 2. Sin embargo, se necesitan más estudios con una preparación bien diseñada y estandarizada para enfatizar el efecto del *Aloe vera* en el control de la glucosa en sangre.

Palabras Clave: *Aloe vera*; hiperglucemia; meta-análisis; revisiones sistemáticas.

ARTICLE INFO
Received: Marzo 9, 2022.
Accepted: June 11, 2022.
Available Online: July 2, 2022.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to either insulin resistance, insufficient insulin secretion or both (ADA, 2014). Diabetes mellitus can be classified into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM), where T2DM is the most common type (90-95%) (ADA, 2019). Diabetes mellitus is a global health threat due to its increasing prevalence and complications (Ogurtsova et al., 2017). It is estimated that the global prevalence of diabetes in 2019 was 9.3%, or 463 million people suffering from diabetes, while the prevalence was projected to be 10.2% (578 million) in 2030 and 10.9% (700 million) in 2045 (Saeedi et al., 2019). Meanwhile, pre-diabetes, a condition with higher blood sugar levels but not high enough to be classified as diabetes, continues to increase, and its global prevalence reached 20.2% (Bansal, 2015; Hostalek, 2019). Moreover, people with uncontrolled pre-diabetes could eventually develop diabetes leading to several complications, including retinopathy, nephropathy and neuropathy (Fareed et al., 2017; Tabák et al., 2012).

Chemical drugs which are currently used to control blood sugar may generate side effects, including liver toxicity, weight gain, and increasing the risk of other cardiovascular diseases (Krass et al., 2017). In addition, long-term use of antidiabetic drugs could induce kidney damage and increase the risk of cancer by 1.3 times (But et al., 2014). On the other hand, the treatments and preventions of diabetes and pre-diabetes are essential to improve well-being and reduce economic costs (Dall et al., 2010). Thus, food-based therapy, which is less likely to cause side effects and more sustainable, is recommended as an alternative treatment (Pandey et al., 2011).

Aloe vera is a medicinal plant that has been used for centuries as an antihyperglycemic agent that could be part of diabetes and pre-diabetes treatment (Ezuruike and Prieto, 2014; Kumar et al., 2019). It has been reported to have beneficial effects on blood glucose control and insulin sensitivity (Febria and Afnuhazi, 2019). Several chemical compounds, chromium, and alprogen, abundantly found in *Aloe vera*, can restore the function of damaged pancreatic beta-cells and insulin activity and lower blood glucose levels (Alinejad-Mofrad et al., 2015).

However, there is still a gap in previous studies regarding the effect of *Aloe vera* in lowering blood glucose and preventing the development of diabetes mellitus. A randomized controlled trial among T2DM patients showed no significant reduction after receiving *Aloe vera* supplements (1000 mg/day) for two months (Zarrintan et al., 2015). A previous meta-analysis evaluating the effect of *Aloe vera* on glycemic control indicates that limited evidence exists and needs further exploration, such as appropriate dose, duration, preparation, and other possible factors (Suksomboon et al., 2016; Zhang et al., 2016). Moreover, additional trials have been recently published (Ariska, 2019; Malinti and Jael, 2019; Ryan et al., 2011; Surya et al., 2020) that can be used to ultimately summarize the effect of *Aloe vera* on blood glucose levels. Therefore, the purpose of this meta-analysis is to compare and summarize the studies on the effect of *Aloe vera* on fasting blood glucose (FBG) among patients with pre-diabetes and T2DM considering moderator variables, such as subjects' characteristics, diagnosis status, dose, duration, preparation, and country of origin.

MATERIAL AND METHODS

Search strategy

PubMed, Scopus, Springer Link, Science Direct, Proquest, and Google Scholar were used to search for the clinical trial studies evaluating the effects of *Aloe vera* on either pre-diabetes, T2DM or both published between 2011 and 2021. The structured search strategy used the following keywords: "aloe" OR "aloe vera gel" OR "aloe vera extract" AND "blood glucose" OR "blood sugar" OR "fasting blood sugar" AND "pre-diabetes" OR "pre-diabetes" OR "type 2 diabetes". The PICO was used to organize the search of this review (Populations: patients with pre-diabetes and T2DM; Intervention: *Aloe vera*; Comparison: control or placebo; Outcomes: FBG). In addition, the search used titles with medical subjects heading (MeSH) and was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Moher et al., 2009).

Inclusion criteria

The classification of pre-diabetes or T2DM was based on American Diabetes Association (ADA) guidelines. Studies were included in the meta-analysis if they met the following criteria: (1) the study was original research with a clinical trial design evaluating the effect of *Aloe vera* on FBG in pre-diabetes and/or T2DM; (2) the study provided the data of the mean FBG and standard deviation (SD) in both control and intervention group; (3) *Aloe vera* was used as the only intervention; (4) the study was published between 2011 and 2021, and in English text. Studies were excluded if published in a proceeding and not in a complete article. We did not limit the

characteristics of the subjects: age, sex, race, weight, and body mass index (BMI). Also, we did not apply language restrictions.

Data extraction and quality assessment

Data were extracted, and quality was assessed independently by four investigators. The data were pooled using standardized and pre-piloted forms following categories: (1) study characteristics, including the last name of the first author, publication year, design, type of diagnosis, age of the subject, dose, duration of intervention, preparation type, and country; and (2) mean FBG and SD of control and intervention group. Disagreement in the extraction was resolved by discussion. The quality of the study was assessed both qualitatively and quantitatively using a rigor score. Each study was assessed using an 8-item-scale plus 1 item regarding the sample size (≥30 participants). Each assessment criteria were given a score of 1 (one) if "yes" and 0 (zero) if "no". In addition, we attempted to find the original data source from the authors to anticipate the unclear or incomplete data.

Statistical evaluation

The meta-analysis was performed using open MEE software (Version 15.4). Treatment effects were determined as the standardized mean difference with a 95% Confidence Interval (CI). Heterogeneity across the studies was detected by calculating I^2. Otherwise, the random-effects model was used because heterogeneity existed. Thus, subgroup analysis was performed within potential sources of heterogeneity, including subjects' characteristics (age, gender, and BMI), duration of intervention, dose, type of preparation, and origin. Funnel plots and Fail Safe-N were used to assess publication bias using JASP software (version 0.15.0).

RESULTS

Results of the literature search

A total of 214 articles were initially obtained, and 152 articles were excluded because of either duplication or irrelevant to the present meta-analysis after carefully reviewing the titles and abstracts, thus leaving 62 articles. Among these 62 articles, 10 articles were not retrieved due to some reasons, including missing data (two articles), investigating T1DM (three articles), a systematic review (one article), and a non-placebo-controlled study (four articles). Furthermore, 52 articles were used for an in-depth examination of eligibility. After assessing the eligibility, 40 articles were excluded for some reasons: six articles were conducted not on humans, 13 articles involved another intervention, and 20 articles were not clinical trials. Thus, 13 articles were ultimately included in the meta-analysis (Alinejad-Mofrad et al., 2015; Ariska, 2019; Arora et al., 2009; Choi et al., 2013; Choudhary et al., 2014; Devaraj et al., 2013; Fallah Huseini et al., 2012; Foadoddini and Alinejad Mofrad, 2020; Huseini et al., 2012; Jubee et al., 2018; Malinti and Jael, 2019; Surya et al., 2020; Zarrintan et al., 2015) (Fig. 1).

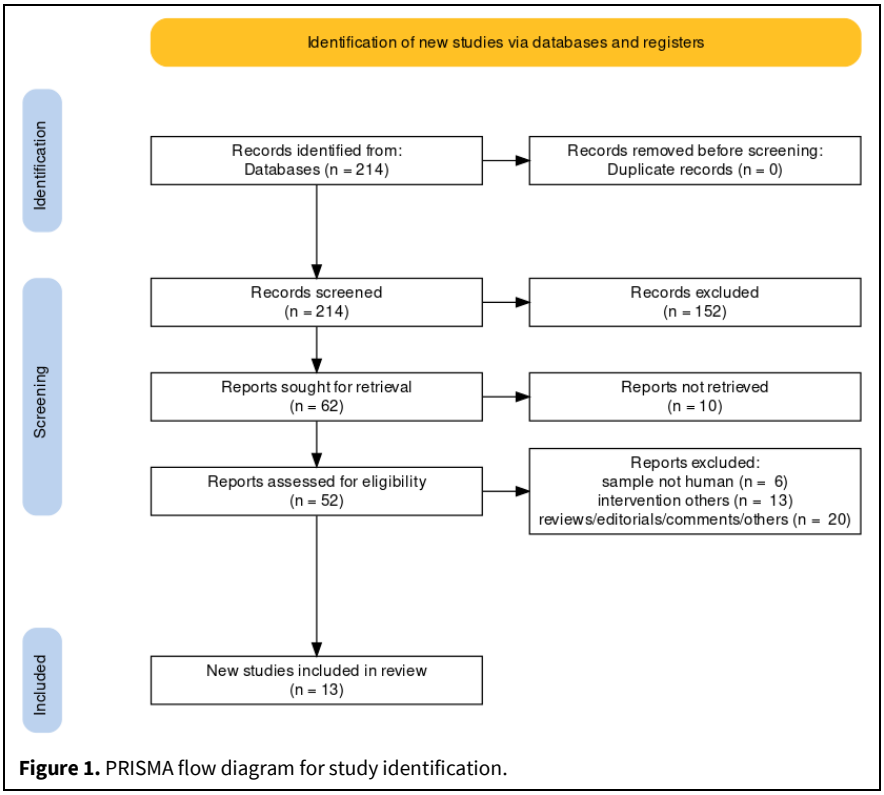

Figure 1. PRISMA flow diagram for study identification.

Table 1. Characteristics of studies included in the meta-analysis.

Reference	N treatment/ control	Study design	Population	Duration (week)	Dosage	Type of preparation	Country
Alnejad-Mofrad et al., 2015 (1)	23/23	RCT	Prediabetes, 35-65 years of age	4	300 mg	Capsule	Iran
Alnejad-Mofrad et al., 2015 (2)	24/23	RCT	Prediabetes, 35-65 years of age	4	500 mg	Capsule	Iran
Alnejad-Mofrad et al., 2015 (3)	23/23	RCT	Prediabetes, 35-65 years of age	8	300 mg	Capsule	Iran
Alnejad-Mofrad et al., 2015 (4)	24/23	RCT	Prediabetes, 35-65 years of age	8	500 mg	Capsule	Iran
Choi et al., 2013 (1)	60/62	RCT	Prediabetes, ≥ 20 years of age	4	700 mg	Capsule	Korea
Choi et al., 2013 (2)	60/62	RCT	Prediabetes, ≥ 20 years of age	8	700 mg	Capsule	Korea
Zarrintan et al.,2015 (1)	21/22	RCT	T2DM, 30-65 years of age	8	1000 mg	Capsule	Iran
Zarrintan et al.,2015 (2)	21/22	RCT	T2DM, 30-65 years of age	8	1000 mg	Capsule	Iran
Choudhary et al., 2014 (1)	30/30	Non-RCT	T2DM, 35-65 years of age	8	100 mg	Capsule	India
Choudhary et al., 2014 (2)	30/30	Non-RCT	T2DM, 35-65 years of age	8	100 mg	Capsule	India
Choudhary et al., 2014 (3)	30/30	Non-RCT	T2DM, 35-65 years of age	12	200 mg	Capsule	India
Choudhary et al., 2014 (4)	30/30	Non-RCT	T2DM, 35-65 years of age	12	200 mg	Capsule	India
Joseph et al., 2018 (1)	25/25	Non-RCT	T2DM, 40-65 years of age	2	20 mL	Juice	India
Joseph et al., 2018 (2)	25/25	Non-RCT	T2DM, 40-65 years of age	4	20 mL	Juice	India
Foadoddini et al., 2020 (1)	24/24	RCT	Prediabetes, 35-65 years of age	8	300 mg	Capsule	Iran
Foadoddini et al., 2020 (2)	24/24	RCT	Prediabetes, 35-65 years of age	8	500 mg	Capsule	Iran
Devaraj et al., 2012 (1)	15/15	RCT	Prediabetes, 19-70 years of age	8	500 mg	Gel powder	USA
Devaraj et al., 2012 (2)	15/15	RCT	Prediabetes, 19-70 years of age	8	500 mg	Gel powder	USA
Arora et al., 2009	12/12	RCT	T2DM, age not mentioned	12	150 ml	Juice	India
Huseini et al., 2011	30/30	RCT	T2DM, 40-60 years of age	8	300 mg	Capsule	Iran
Ariska et al., 2019	11/11	Non-RCT	T2DM, 29-57 years of age	2	100 mg	Decoction	Indonesia
Huseini et al., 2012	35/35	RCT	T2DM, 40-60 years of age	8	300 mg	Gel powder	Iran
Malinti and Jael 2019 (1)	15/15	Non-RCT	Prediabetes, 30-60 years of age	1	100 mg	Gel	Indonesia
Malinti and Jael 2019 (2)	15/15	Non-RCT	Prediabetes, 30-60 years of age	1	200 mg	Gel	Indonesia
Surya et al., 2020	22/22	RCT	T2DM, > 20 years of age	2	300 mL	Juice	Indonesia

The number in parentheses shows the trial arm in one study

Study characteristics

Twenty-five trial arms reported in 13 publications were included, with a total of 642 subjects in the treatment group. Among the included publications, eight were conducted by randomized-controlled trials, while the rest did not perform randomization. In addition, five trials were performed in prediabetic patients, whereas eight trials in diabetic patients. The publication came from several countries, including Iran (five articles), Korea (one article), India (three articles), USA (one article), and Indonesia (three articles). The duration of the intervention varied from one week to 12 weeks, and the intervention was mostly performed for eight weeks. Also, various dosage regimes of intervention were found (100–1000 mg; 20–300 mL). Meanwhile, the capsule was the type of intervention that was mainly used (Table 1).

Overall analysis

The result of the present meta-analysis showed a significant reduction in FBG among prediabetic and diabetic patients administered with *Aloe vera* by -1.035 mg/dL (95% CI, -1.454, -0.616) compared with control ($p<0.001$) (Fig. 2). However, there was significant heterogeneity between trials (I^2 = 91.37%, $p<0.001$), thus, the effect size was obtained from a random-effect model. Furthermore, subgroup analysis was performed to investigate further the effects of subjects' characteristics (age, gender, and BMI), diagnosis status, duration of intervention, *Aloe vera* dosage, type of preparation, and country of origin.

Subgroup analysis

Subjects' characteristics, including age, gender, and BMI, were used in subgroup analysis. However, several studies did not completely provide the data, so the analysis might not include those studies. The

present meta-analysis found that the effect of *Aloe vera* on FBG was still significant in both subjects under (FBG: -1.097 [-2.136, -0.057] mg/dL; p<0.001) and over (FBG: -1.015 [-1.486, -0.544] mg/dL; p<0.001) 30 years compared to control (Fig. 3A). Moreover, the significant effect was remarkably observed in male (FBG: -2.954 [-4.198, -1.710] mg/dL; p<0.001) (Fig. 3B). Among subjects with BMI 25 to 30 kg/m^2, the effect was still significant (FBG: -1.267 [-1.847, -0.687] mg/dL; p<0.001), but it was not significant among subjects with BMI over 30 kg/m^2 (Fig. 3C). Unfortunately, significant heterogeneity was still observed even after subgroup analysis adjusting their subject's characteristics.

The subgroup analysis then found the significant effect of *Aloe vera* on FBG in both prediabetes (FBG: -0.821 [-1.417, -0.224] mg/dL; p<0.01) and T2DM (FBG: -1.238 [-1.853, -0.623] mg/dL; p<0.01) compared to control (Fig. 4A). In addition, the more favorable effect was found in T2DM. The result also showed that both short (<8 week) (FBG: -0.838 [95% CI, -1.345, -0.331] mg/dL; p<0.001) and long-term intervention (≥8 weeks) (FBG: -1.147 [95% CI, -1.1751, -0.543] mg/dL; p=0.001) significantly reduced FBG compared to control group (Fig. 4B). Moreover, a bigger effect size was achieved in long-term intervention. Among seven doses of capsule (100, 200, 300, 500, 700, 1000 mg), only dose of 200 mg (FBG: -3.835 [95% CI, -4.810, -2.860] mg/dL; p=0.01), and 700 mg (FBG: -0.438 [95% CI, -2.856, -1.140] mg/dL; p=0.01) remained significant, whereas the significant difference also found in others dose (FBG: -0.940 [95%CI, -1.383, -0,496] mg/dL; p=0.003) (Fig. 4C). Dose of 200 mg provided the bigger effect size while high heterogeneity was still found. The intervention with capsule and juice still showed significant reduction in FBG with the effect size of -1.087 [95% CI, -1.565, -1.140] mg/dL (p=0.01), FBG: -0.782 [95% CI, -1.099, -0.465] mg/dL; (p=0.01), respectively. However, others type of *Aloe vera* preparation did not show significant reduction (FBG: -1.035 [95% CI, -2.086, 0.17] mg/dL; p=0.054) (Fig. 4D). In addition, only study from India (FBG: -2.089 [95% CI, -3.032, -1.145] mg/dL; p<0.01) and Korea (FBG: -1.998 [95% CI, -2.856, -1.140] mg/dL; p<0.01) showed the significant reduction, which indicates variations between the countries (Fig. 4E).

Publication bias

Funnel plots showed symmetrical results, which indicated no publication bias (Fig. 5). The results of fails-safe N value calculation also showed no publication bias (N value = 2177, >K = 135).

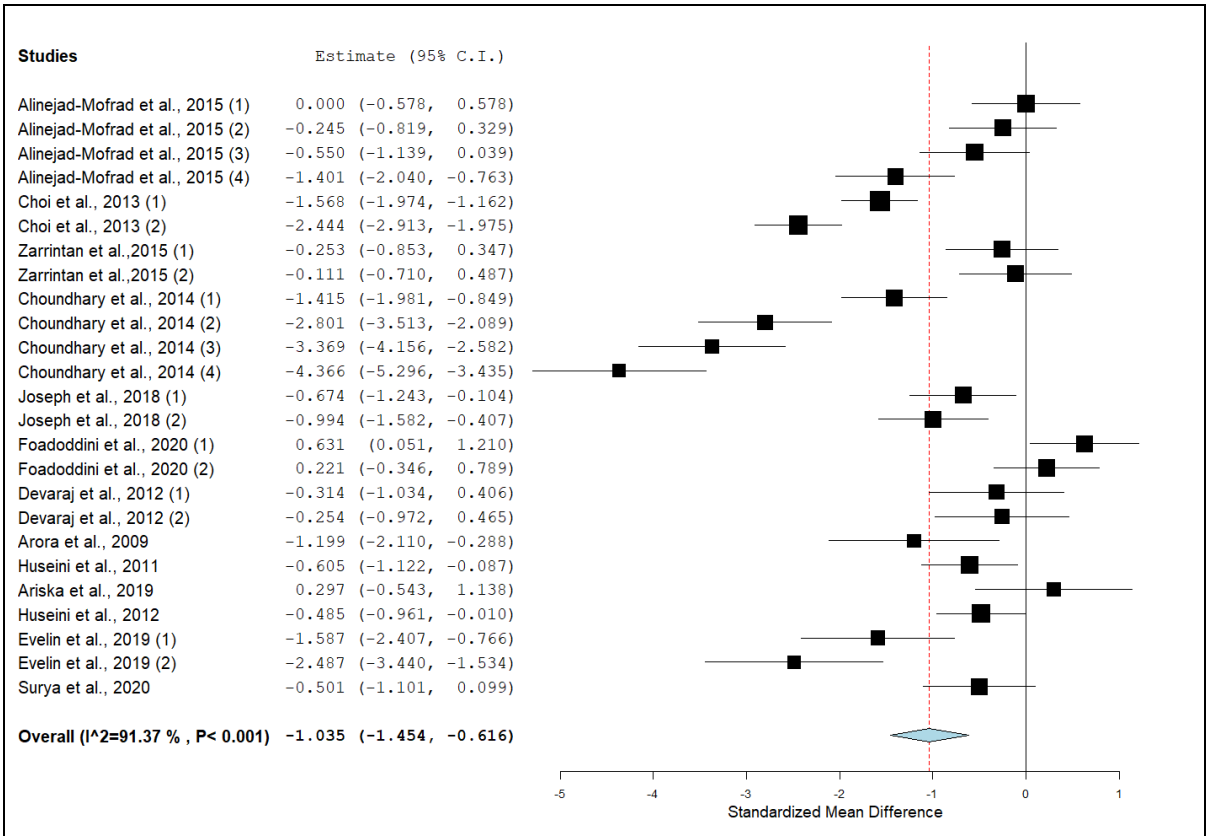

Figure 2. Forest plot of studies that evaluated the effect of *Aloe vera* on fasting blood glucose compared to control. Each study is represented by a block. Each square represents the standardized mean difference with a 95% confidence interval indicated by a horizontal line. Square size is proportional to the precision of the study.

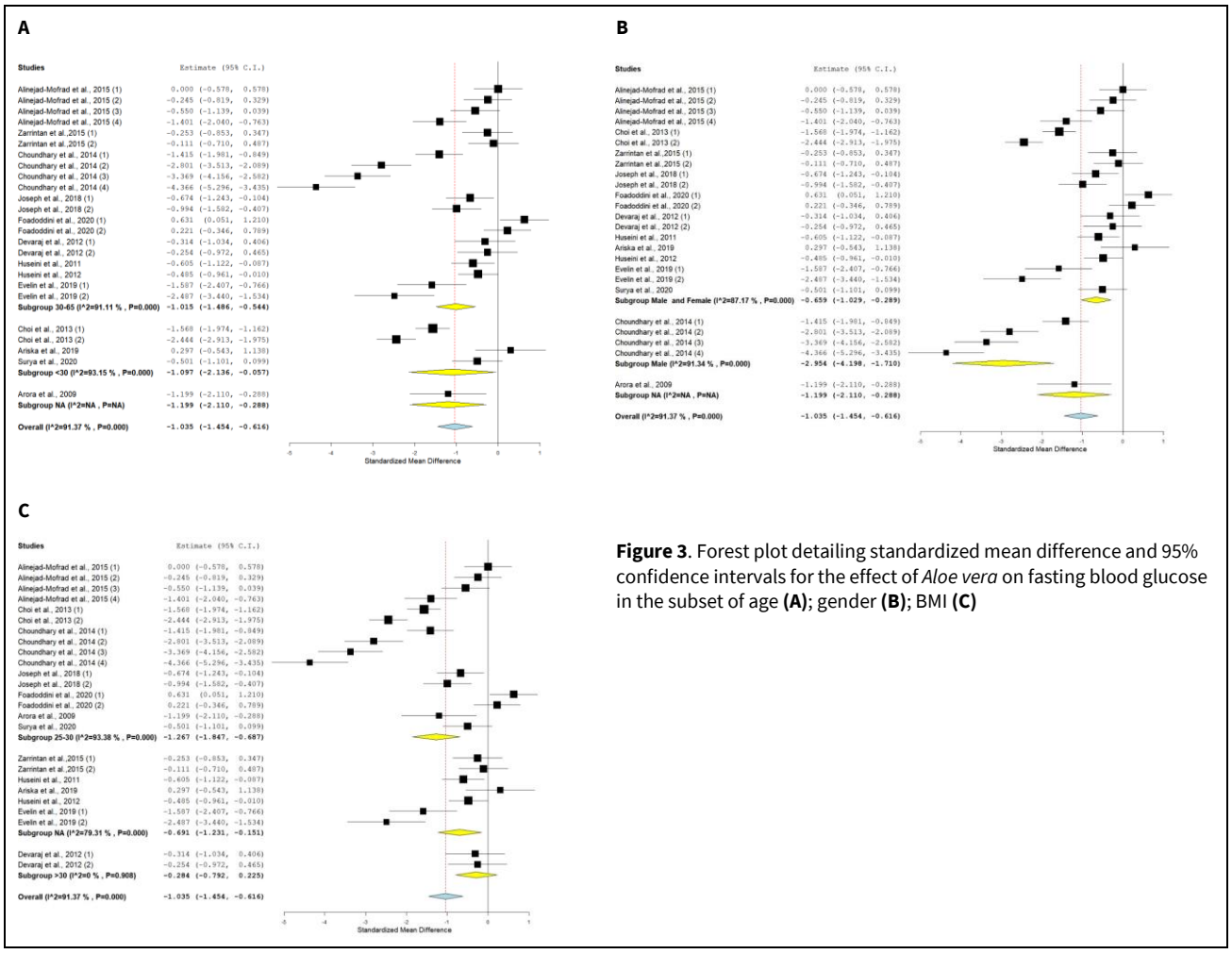

Figure 3. Forest plot detailing standardized mean difference and 95% confidence intervals for the effect of *Aloe vera* on fasting blood glucose in the subset of age **(A)**; gender **(B)**; BMI **(C)**

DISCUSSION

Aloe vera has been extensively used as a medicinal plant due to its wide range of therapeutic effects (Sahu et al., 2013). The present meta-analysis demonstrated that *Aloe vera* significantly lowered FBG in prediabetic and diabetic patients. We found a significant effect in all groups of age, whereas among male subjects with a BMI of 25 to 30 kg/m^2, the effect was more remarkable. Moreover, the significant reduction in FBG was only observed when *Aloe vera* was administered in the form of a capsule or juice and a dose of 200 mg or 700 mg. Meanwhile, both short (<8 weeks) and long-term intervention (≥8 weeks) showed a significant reduction, where long-term intervention revealed a more obvious effect size. Nonetheless, the country of origin may influence the effect of *Aloe vera* on FBG, where a significant reduction was only found in India and Korea.

The overall result of this meta-analysis was consistent with the results in diabetic animal models demonstrating beneficial effects of *Aloe vera* in glycemic control (Afaf et al., 2008; Manjunath et al., 2016; Okyar et al., 2001; Rajasekaran et al., 2006). Two previous meta-analyses similarly demonstrated a significant reduction of FBG, although those meta-analyses reported limited evidence (Suksomboon et al., 2016; Zhang et al., 2016). Indeed, the present meta-analysis supports and emphasizes the beneficial effects of *Aloe vera*. Otherwise, heterogeneity across publications was still significant in most cases (I^2 > 50%). Heterogeneity might exist due to the extent of variation in magnitudes or opposite direction of effect caused by several potential sources of heterogeneity, such as country of origin, population, and methodology (Chen et al., 2012; Sedgwick, 2015). Thus, a random effect model and subgroup analysis were conducted (Huedo-Medina et al., 2006).

The subgroup analysis involving subjects' characteristics revealed that *Aloe vera* was effective in reducing FBG in all age groups. The effect of *Aloe vera* on male subjects showed a more significant result. In contrast with males, females may have several menopause episodes and a high risk of obesity which exaggerate T2DM, thus lowering the effect of *Aloe vera* (Slopien et al., 2018). However, we could only extract the male group in this study. As our study did not find a significant effect among subjects with BMI over

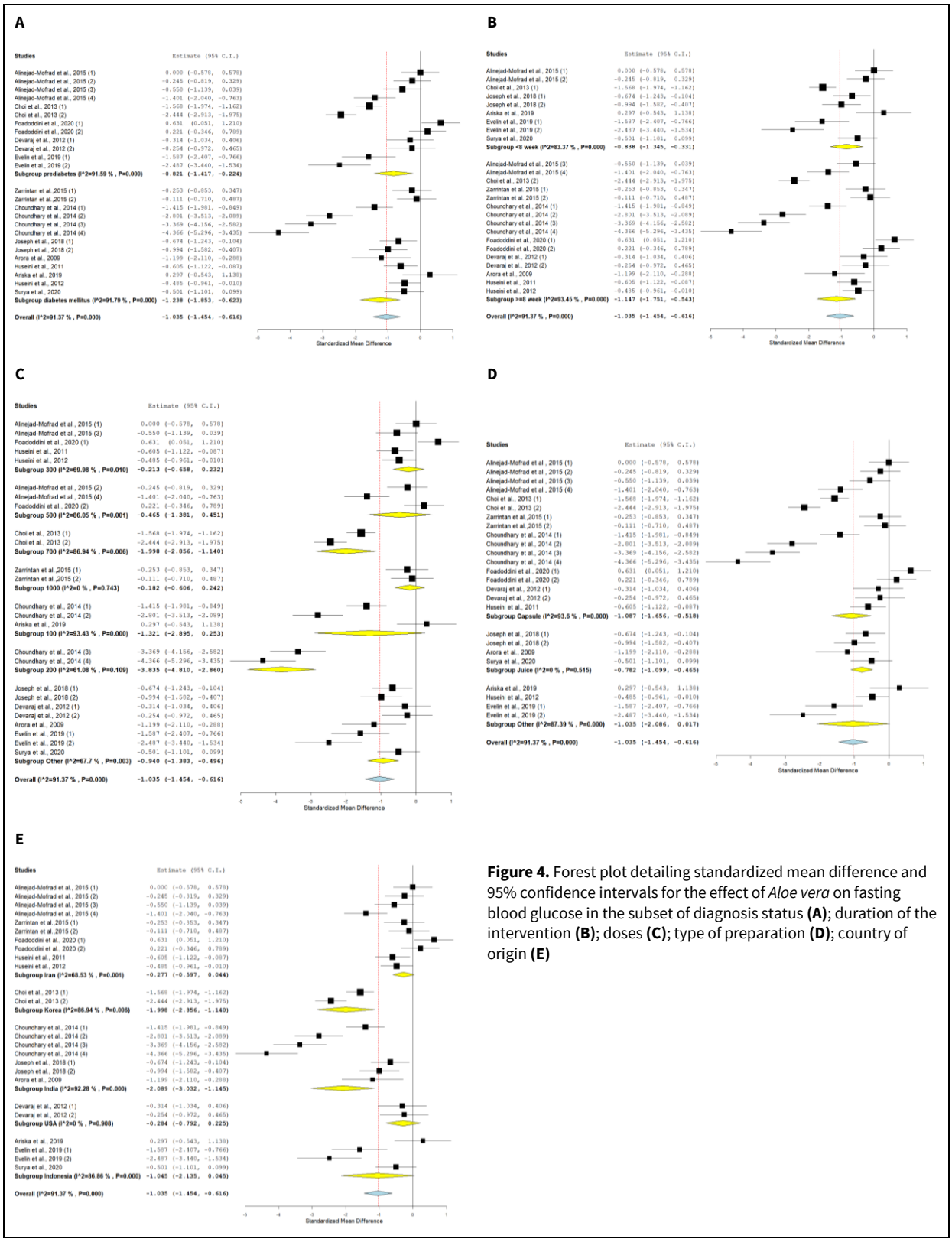

Figure 4. Forest plot detailing standardized mean difference and 95% confidence intervals for the effect of *Aloe vera* on fasting blood glucose in the subset of diagnosis status **(A)**; duration of the intervention **(B)**; doses **(C)**; type of preparation **(D)**; country of origin **(E)**

30 mg/kg[2], obesity has been linked as a major risk factor for diabetes (Zhang et al., 2019). High body fat composition causes increased amounts of free fatty acids and proinflammatory cytokines, leading to insulin resistance (Kahn et al., 2006).

Further subgroup analysis showed *Aloe vera* significantly reduced FBG in patients with both prediabetes and T2DM where the effects were found more remarkable in T2DM. A previous study also found that the administration of medicinal plants

significantly affected blood glucose more in T2DM than in pre-diabetes (Poolsup et al., 2019). Moreover, a longer duration of intervention demonstrated a bigger effect size, although both durations showed significant reduction (min: 1 week; max: 12 weeks). Appropriate duration of the intervention is needed to generate a meaningful effect, while a short period of intervention may not be enough to cause a significant effect (Nair, 2019). On the other hand, information regarding long-term *Aloe vera* consumption safety is still unclear; hence, prolonged consumption needs attention (Zhang et al., 2016).

Muscle weakness, abdominal pain, and cramping have been reported as side effects of *Aloe vera* (Surjushe et al., 2008). Likewise, the present meta-analysis failed to show a dose-response relationship between *Aloe vera* consumption and FBG. Only a slightly low (200 mg) and slightly high (700 mg) dose significantly reduced FBG compared to control. Meanwhile, a slightly low dose generated the biggest effect. Various daily dosages with different duration and forms of intervention cause it difficult to establish minimum effective dose (Wang et al., 2015). In fact, the low dose might cause lesser side effects leading to higher adherence (Surjushe et al., 2008). Nevertheless, the evidence of both doses was limited. Regarding the other dose subgroup showed a significant reduction; however, we could not conclude the results due to the various dosage units in this group. Moreover, capsule and juice were the type of preparation demonstrating a significant reduction in FBG compared to control. The concentration of *Aloe vera* in both capsule and juice can be controlled and standardized accurately, whereas it was not in gel and decoction. In addition, high temperature in the decoction method could reduce bioactive components in *Aloe vera* leading to lower biological activities (Wojdyło et al., 2021). This study then revealed the differences of effect size across the countries. The studies where performed in India showed more considerable effect. This was probably caused by the longer duration (mostly 12 weeks) and fully performed in T2DM as the present findings and the previous study showed medicinal plant generated more obvious effect on blood glucose control in T2DM than in pre-diabetes (Poolsup et al., 2019).

Several mechanisms of action have been proposed to explain the association between *Aloe vera* and glycemic control. *Aloe vera* could attenuate carbohydrate absorption due to high fiber content leading to lowered glucose production and enhanced glucose storage and utilization (Akpan et al., 2014; Misawa et al., 2012; Rajasekaran et al., 2005). High molecular weight polysaccharides and or phytosterol isolated from *Aloe vera* gel could exhibit glucose transport enhancement indicated by blood glucose uptake improvement and serum cholesterol reduction (Anand et al., 2010; Beppu et al., 2006). Another theory is that *Aloe vera* could inhibit adipogenesis through AMPK activation and obesity-related inflammation, resulting in increased insulin sensitivity (Shin et al., 2011). In addition, aloe emodin-8-O-glycoside, an anthraquinone isolated from *Aloe vera*, has been reported to improve insulin signaling cascade and glycogen storage through activation of phosphatidyl inositol 3′ kinase (PI3K) and insulin receptor beta IRβ (Anand et al., 2010).

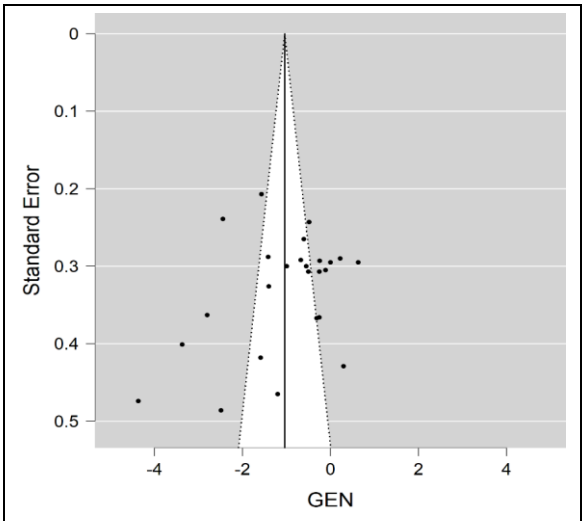

Figure 5. Funnel plots of trials included in the meta-analysis of the effect of *Aloe vera* on fasting blood glucose.

Before recommending the results to health professionals, some limitations of the present meta-analysis should be highlighted and considered. We still found a high heterogeneity across the studies, where the previously published meta-analysis also obtained the same results (Suksomboon et al., 2016; Zhang et al., 2016). The current meta-analysis included both RCT and non-RCT studies, which would provide a poor-quality trial. In addition, both pharmacological and non-pharmacological therapies that diabetic patients used make it difficult to differentiate the effect of *Aloe vera* alone. Otherwise, this meta-analysis included more trials than the previous meta-analysis and considered some factors that possibly influenced the effect of *Aloe vera* on FBG.

CONCLUSION

The currently available data suggest that *Aloe vera* may reduce FBG in pre-diabetes and diabetes. The significant effect was observed in all age groups and was found more remarkable in male subjects with BMI not more than 30 mg/kg^2. However, significant heterogeneity was still found, and the study results failed to confirm the dose-response relationship. Variation results were also still observed between the

countries. Therefore, further study with standardized preparation and rigorously designed is needed to clarify the effect of *Aloe vera* in managing pre-diabetes and T2DM.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Authors acknowledge Cross-Country Lecturer Collaboration (CEL-KODELN) for providing a workshop on a meta-analysis, which this manuscript is one of the outputs. Also, the authors thank Prof. Hari Basuki and Prof. Asnawi Abdullah for comments that improved the manuscript. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Contribution	Budiastutik I	Subagio HM	Kartasurya MI	Widjanarko B	Soegiyanto	Kartini A	Suhartono S
Concepts or ideas	x	x					x
Design	x	x	x	x	x	x	x
Definition of intellectual content		x	x		x		
Literature search	x	x		x			x
Experimental studies	x	x		x			x
Data acquisition	x	x	x	x	x	x	x
Data analysis	x	x	x	x	x	x	x
Statistical analysis	x	x	x	x	x	x	x
Manuscript preparation	x	x	x	x	x	x	x
Manuscript editing	x	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x

Citation Format: Budiastutik I, Subagio HM, Kartasurya MI, Widjanarko B, Soegiyanto, Kartini A, Suhartono S (2022) The effect of *Aloe vera* on fasting blood glucose levels in pre-diabetes and type 2 diabetes mellitus: A systematic review and meta-analysis. J Pharm Pharmacogn Res 10(4): 737–747. https://doi.org/10.56499/jppres22.1378_10.4.737