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Meta-analysis

Effect of *Zingiber officinale* Rhizome Powder on Fasting Blood Sugar Levels and HbA1c in Type 2 Diabetes Mellitus Patients: A Meta-Analysis

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ABSTRACT

Background: Diabetes mellitus (DM) type 2 is the most common type of diabetes caused by insulin resistance and relative deficiency of insulin secretion. Several studies have shown inconsistent results regarding the effect of *Zingiber officinale* powder in patients with type 2 DM. As a result of these inconsistencies, researchers are compelled to prove the effect of Zingiber officinale powder on fasting blood sugar (GDP) and HbA1c levels in type 2 DM patients through a meta-analysis study.
Subject and Method: This study is a meta-analysis of a number of randomized controlled trials. The articles were obtained from the PubMed, Science Direct, Springerlink and Google Scholar databases published in 2012-2022. The search articles were carried out by considering the feasibility of the criteria determined using the PICO model. Population: type 2 DM patients, Intervention: *Zingiber officinale* rhizome powder, Comparison: placebo, Outcome: GDP and HbA1c levels. The keywords used are "*Zingiber officinale*" OR "Zingiber" OR "*Z. officinale*" OR "Ginger" AND "Fasting blood glucose" AND "HbA1c" OR "A1c" OR "Glicemic" OR "Glucose" OR "Diabetes Mellitus" OR "type 2 diabetes mellitus" AND "Randomized Controlled Trial". Article selection with PRISMA flow diagram. Analysis of articles using the Revman 5.3 application.
Results: A total of 11 articles were reviewed in this study. Analysis of 11 articles showed that administration of *Zingiber officinale* rhizome powder could significantly reduce GDP levels in type 2 DM patients (Standardized Mean Difference (SMD)= -0.79; 95% CI= -1.32 to -0.26; p= 0.004). Analysis of 10 articles showed that administration of *Zingiber officinale* rhizome powder could significantly reduce HbA1c levels (SMD = -0.38; 95% CI= -0.55 to -0.22; p<0.001).
Conclusion: Zingiber officinale rhizome powder can significantly reduce GDP and HbA1c levels in type 2 DM patients.

Keywords: *Zingiber officinale*, diabetes mellitus tipe 2, GDP, HbA1c

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BACKGROUND

Diabetes mellitus (DM) is a heterogeneous metabolic disorder whose main finding is chronic hyperglycemia. Causes include impaired insulin secretion or impaired insulin effect or both (ADA, 2010; Petersmann et al., 2019). DM disease is divided into four types based on the cause, namely type 1 DM, type 2 DM, DM due to pregnancy (gestational), and other types of DM (PERKENI, 2019). Diabetes mellitus (DM) type 2 is the most common type of diabetes caused by

insulin resistance and a relative deficiency of insulin secretion (Solis-Herrera et al., 2018).

The global diabetes prevalence in 2021 is around 10.5% (536.6 million people) and will increase to 11.3% (642.7 million) in 2030 and 12.2% (783.2 million) in 2045. According to data from the International Diabetes Federation (IDF) in 2021, Indonesia ranks fifth among countries with the highest number of DM sufferers, namely 19.5 million (IDF, 2021; Ministry of Health, 2020). Based on the 2018 Basic Health Research (Riskesdas) the prevalence of DM in Indonesia based on a doctor's diagnosis at the age of 15 years was 2%, an increase of 0.5% compared to Riskesdas in 2013 (Kemenkes RI, 2019).

Diabetes is a leading cause of blindness, kidney failure, heart attacks, strokes and lower limb amputations. Between 2000 and 2016, there was a 5% increase in premature death from diabetes. In 2019, diabetes was the ninth leading cause of death with an estimated 1.5 million deaths directly attributable to diabetes (WHO, 2021).

Diagnosis of diabetes mellitus can be confirmed by checking fasting blood sugar (GDP) and HbA1c. The patient was diagnosed with DM if the GDP level was 126 mg/dl or the HbA1C level was 6.5%. DM management by implementing a healthy lifestyle and administering anti-diabetic drugs (OAD) or insulin (PERKENI, 2019). The use of natural ingredients such as ginger rhizome (Zingiber officinale) also has the potential to be used for the management of DM.

Zingiber officinale is commonly known as ginger. According to the botanical classification, Zingiber officinale belongs to the Zingiberaceae family originating from Southeast Asia. The rhizome of Zingiber officinale is often used as a spice throughout the world for culinary and medicinal purposes. Zingiber officinale has been widely used in Chinese medicine, Ayurveda, and has complemented centuries-old herbal therapies for various ailments. Ginger powder contains compounds that are useful in controlling blood sugar levels in type 2 DM patients, including gingerol, shogaol, paradol, zingerone, dehydro-10-gingerdione, terpenoids, and flavonoids. Ginger can reduce the activity of -amylase and -glucosidase enzymes in the digestive tract so that sugar absorption decreases. Ginger has antioxidant properties in inhibiting ROS (Reactive Oxygen Species) so that it can prevent damage to pancreatic beta cells. Ginger can inhibit insulin resistance and reduce the homeostatic index of the assessment model for insulin sensitivity (HOMA) and increase the quantitative insulin sensitivity check index (QUICKI) index (Akash et al., 2015).

According to El Gayar's research on 80 DM patients in a randomized controlled trial, it proved that Zingiber officinale can reduce fasting blood sugar levels and HbA1c levels compared to the control group. The results showed that the use of Zingiber officinale powder as much as 1.8 grams for 8 weeks significantly reduced fasting blood sugar ($p<0.001$) and HbA1C ($p<0.001$). So it can be said that Zingiber officinale is considered a safe and effective antidiabetic adjuvant (El Gayar et al., 2019).

Mahluji in his study of 58 DM patients in a randomized controlled trial found different results. According to Mahluji's research, giving 2 grams of Zingiber officinale powder for 8 weeks did not significantly affect fasting blood sugar levels ($p=0.424$) and HbA1c levels ($p=0.664$) compared to the control group. So that giving ginger to DM patients is less useful and further research needs to be done (Mahluji et al., 2013).

Based on the above research showing the inconsistency of research results on the effect of Zingiber officinale rhizome in DM patients, the authors are interested in knowing more about the effect of Zingiber

officinale rhizome powder on GDP and HbA1c levels in type 2 DM patients through a meta-analysis study.

SUBJECTS AND METHOD

1. Study Design

This is a systematic review and meta-analysis. The articles used in this study were obtained from several databases including PubMed, Science Direct, Springerlink and Google Scholar. The keywords to search for articles were as follows: "Zingiber officenale" OR "Zingiber" OR "Z. officinale" OR "Ginger" AND "Fasting blood glucose" AND "HbA1c" OR "A1c" OR "Glicemic" OR "Glucose" OR "Diabetes Mellitus" OR "type 2 diabetes mellitus" AND "Randomized Controlled Trial".

2. Inclusion Criteria

The article is a full paper article with a Randomized Controlled Trial (RCT) design. The research subjects were type 2 diabetes mellitus who received Zingiber officinale powder intervention compared to placebo. The outcome of the study was fasting blood sugar or HbA1c. Articles published in English or Indonesian in 2012-2022.

3. Exclusion Criteria

Articles published in languages other than English or Indonesian. Study design is not an RCT. The study included patients with a diagnosis of type 1 DM, gestational DM, and diabetes due to other factors as subjects.

4. Variable Operational Definition

The search for articles was carried out by considering the eligibility criteria determined using the PICO (Population, Intervention, Comparison, Outcome) model. Population: type 2 DM patients, Intervention: Zingiber officinale rhizome powder, Comparison: placebo, Outcome: GDP and HbA1c levels.

Fasting blood sugar level is an examination of blood sugar levels after not consuming at least 8 hours before the examination.

HbA1c level is a laboratory examination of HbA1c levels in blood plasma, carried out at least 8 weeks after the intervention.

Zingiber officinale powder is powder from the rhizome of Zingiber officinale which is processed in the form of capsules/tablets or other oral preparations.

5. Data Analysis

Data processing is carried out using the Review Manager application (RevMan 5.3) by calculating the effect size and heterogeneity which is a combination of study models and forms a meta-analysis of the final results.

RESULTS

The process of searching for articles through the journal database can be seen in Figure 1. Figure 2 shows the area where articles were taken according to the inclusion criteria. The articles obtained consisted of 11 articles whose research subjects came from Iran, Saudi Arabia, Egypt, and Brazil.

Critical appraisal of each study can be seen in Table 1. An overview of primary studies that meet the requirements for meta-analysis can be seen in Table 2. Assessment of the quality of the study using critical appraisal tools randomized controlled trial (RCT) published by CEBM University Of Oxford 2014:

a. Does the research address clearly focused statements/problems?

b. Is the Randomized Controlled Trial research method appropriate to answer the research question?

c. Are there enough subjects in the study to establish that the findings did not occur by chance?

d. Were subjects randomly allocated to the experimental and control groups? If not, could this be biased?

e. Are inclusion/exclusion criteria used?

f. Were the two groups comparable at the start of the study?
g. Were objective and unbiased outcome criteria used?
h. Are objective and validated measurement methods used in measuring the results? If not, were results assessed by someone who was not aware of the group assignment (ie was the assessment blinded)?
i. Is effect size practically relevant?
j. How precise is the estimate of the effect? Is there a confidence interval?
k. Could there be confounding factors that have not been taken into account?
l. Are the results applicable to your research?

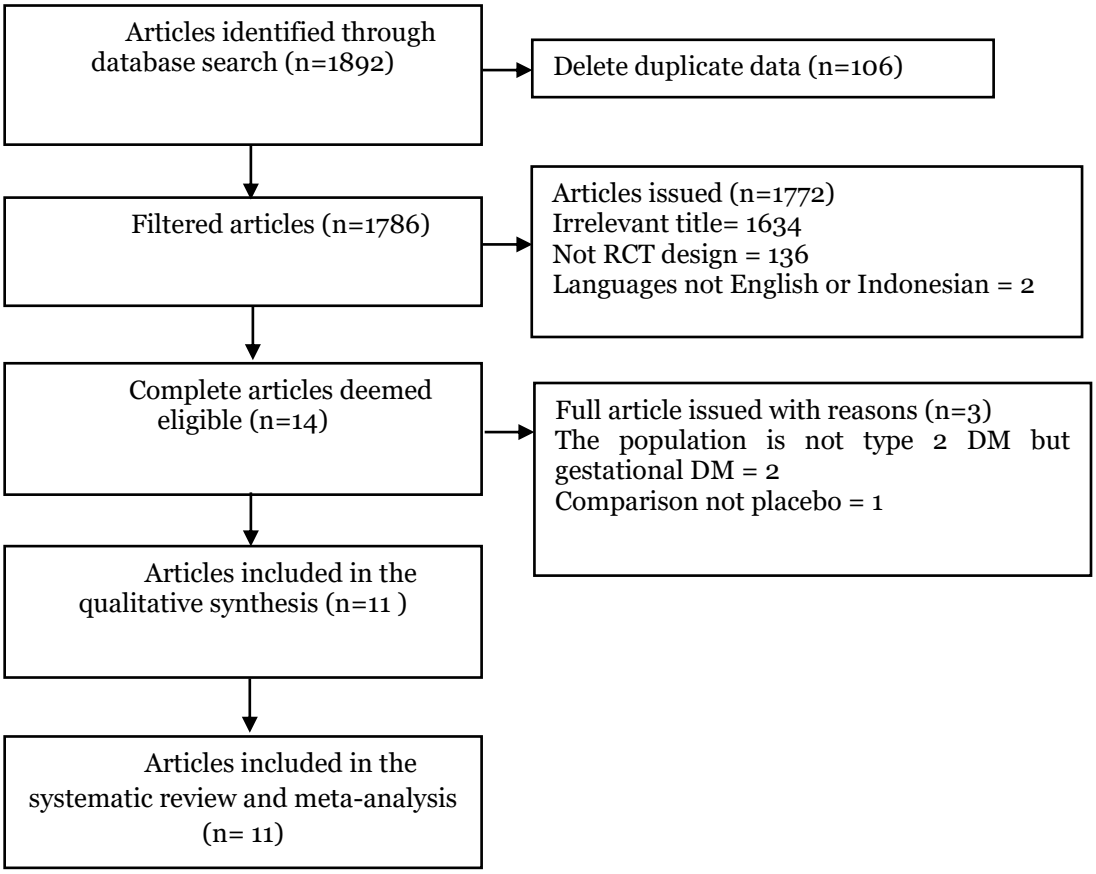

Figure 1: PRISMA Diagram

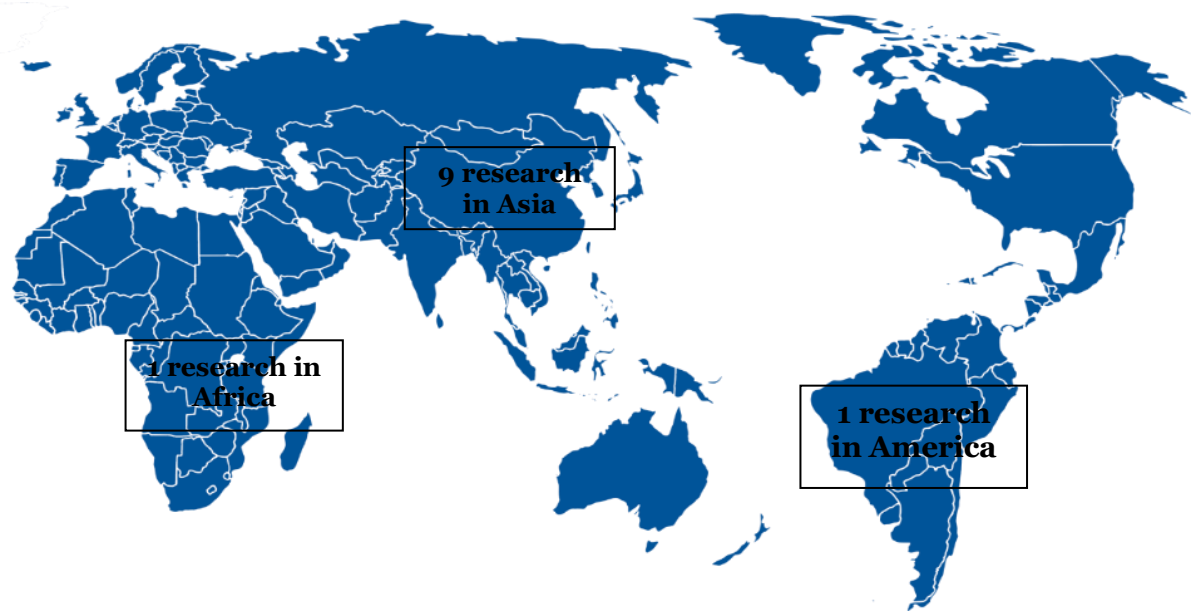

Figure 2. Research area

Table 1. Results of Quality Assessment of Randomized Control Trial Studies

Author (Year)	Criteria											Total
	1	2	3	4	5	6	7	8	9	10	11	
Arablou et al., 2014	1	1	1	1	1	1	0	0	1	1	1	9
Arzati et al., 2017	1	1	1	1	1	1	0	0	1	1	1	9
Carvalho et al., 2020	1	1	1	1	1	1	0	0	1	1	1	9
El Gayar et al., 2019	1	1	0	0	1	1	1	0	1	1	1	8
Elsaadany et al., 2021	1	1	0	1	1	1	1	0	1	1	1	9
Gholinezhad et al., 2020	1	1	1	1	1	1	0	0	1	1	1	9
Khandouzi et al., 2015	1	1	1	1	1	1	0	0	1	1	1	9
Mahluji et al., 2013	1	1	1	1	1	1	0	0	1	1	1	9
Mozaffari-Khosravi et al., 2014	1	1	1	1	1	1	0	0	1	1	1	9
Rahimlou et al., 2019	1	1	1	1	1	1	1	0	1	1	1	10
Shidfar et al., 2015	1	1	1	1	1	1	1	0	1	1	1	10

Table 2. Description of the primary studies that were included in the meta-analysis

Author Name and Year	Country	Study Design	Total of Sample	P *Population*	I Intervention	C Comparison	O Outcome
Arablou *et al.*, 2014	Iran	RCT	I=33 C=30	Type 2 DM patients	1.6 g ginger powder/day for 12 weeks	placebo	GDP and HbA1c
Arzati *et al.*, 2017	Iran	RCT	I=23 C=22	Type 2 DM patients	2 g ginger powder/day for 10 weeks	placebo	GDP and HbA1c
Carvalho *et al.*, 2020	Brazil	RCT	I=47 C=56	Type 2 DM patients	1.2 g ginger powder/ day for 90 days	placebo	GDP and HbA1c
El Gayar *et al.*, 2019	Mesir	RCT	I=40 C=40	Type 2 DM patients	1.8 g ginger powder/ day for 8 weeks	placebo	GDP and HbA1c
Elsaadany *et al.*, 2021	Saudi Arabia	RCT	I=11 C=11	Type 2 DM patients	3 g ginger powder/ day for 8 weeks	placebo	GDP and HbA1c
Gholinezhad *et al.*, 2020	Iran	RCT	I=21 C=21	Type 2 DM patients	2 g ginger powder/ day for 8 weeks	placebo	GDP and HbA1c
Khandouzi *et al.*, 2015	Iran	RCT	I=22 C=19	Type 2 DM patients	2 g ginger powder/day for 12 weeks	placebo	GDP and HbA1c
Mahluji *et al.*, 2013	Iran	RCT	I=28 C=30	Type 2 DM patients	2 g ginger powder/ day for 8 weeks	placebo	GDP and HbA1c
Mozaffari-Khosravi *et al.*, 2014	Iran	RCT	I=40 C=41	Type 2 DM patients	3 g ginger powder/ day for 8 weeks	placebo	GDP and HbA1c
Rahimlou *et al.*, 2019	Iran	RCT	I=19 C=18	Type 2 DM patients	2 g ginger powder/ day for 12 weeks	placebo	GDP
Shidfar *et al.*, 2015	Iran	RCT	I=22 C=23	Type 2 DM patients	3 g ginger powder/ day for 12 weeks	placebo	GDP and HbA1c

a. Forest plot of Zingiber officinale powder on fasting blood sugar levels

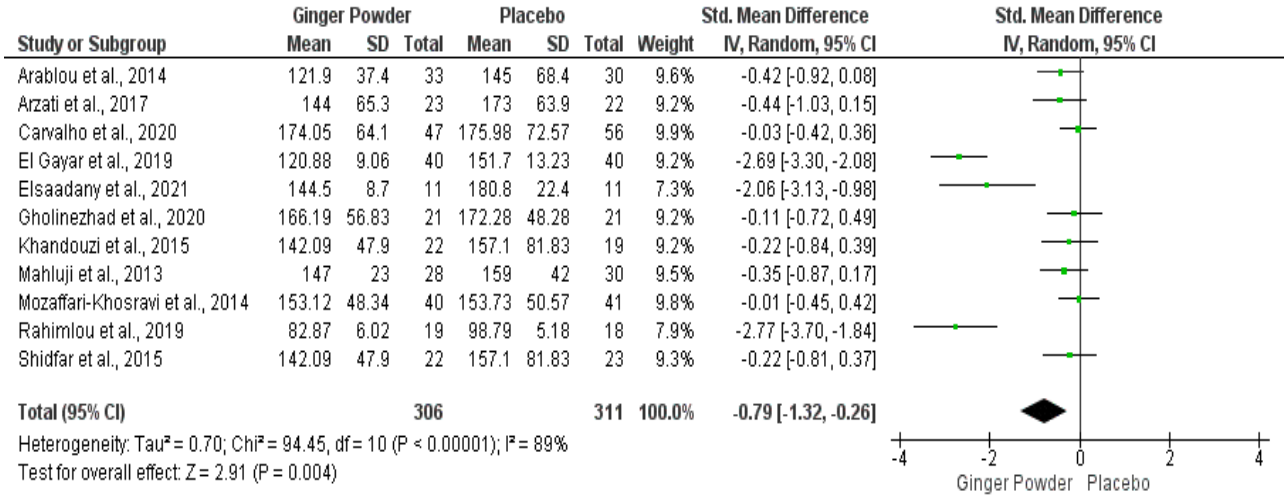

Figure 3. Forest plot of the effect of ginger powder on GDP levels in type 2 DM patients

Figure 3 shows that ginger powder is effective in reducing GDP levels in patients with type 2 diabetes. Type 2 DM patients who received ginger powder experienced a decrease in GDP levels of 0.79 units lower than patients with type 2 diabetes who received a placebo and was statistically significant (Standardized Mean Difference = -0.79; 95% CI= -1.32 to -0.26; p=0.004). The heterogeneity of the research data shows I^2= 89% so that the distribution of the data is declared heterogeneous (random effect model).

b. Funnel plot of Zingiber officinale powder on fasting blood sugar levels

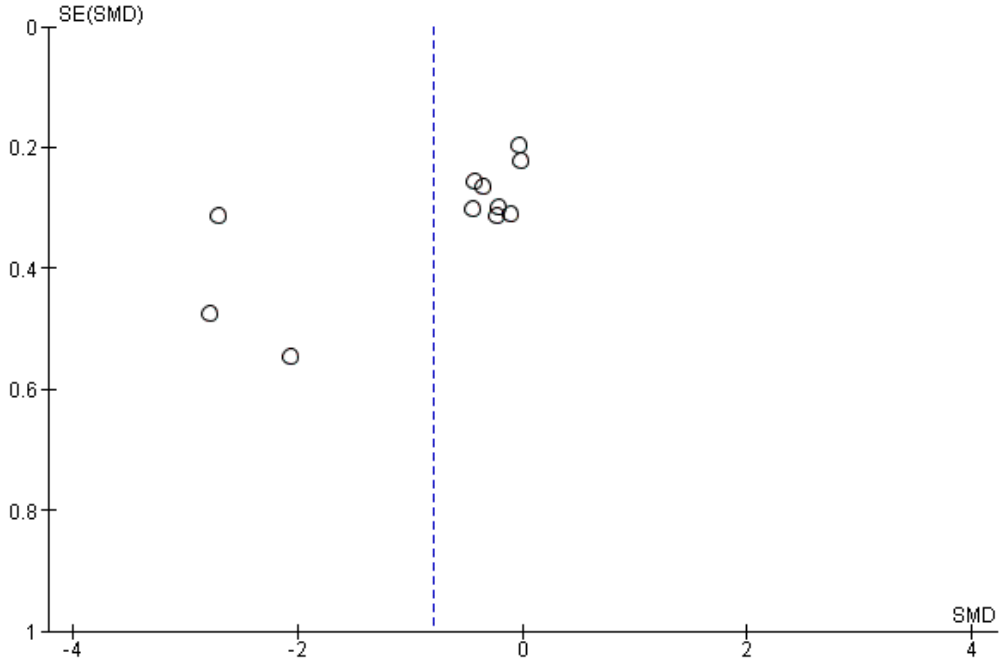

Figure 4. Funnel plot of the effect of ginger powder on GDP levels in type 2 DM patients

Based on Figure 4, there is a publication bias which is indicated by the asymmetry of the right and left plots, where 8 plots are on the right and 3 plots are on the left. The plot on the right of the graph appears to have a standard error (SE) between 0.2 and 0.4. The plot on the left of the graph appears to have a standard error (SE) between 0.3 and 0.6.

c. Forest plot of Zingiber officinale powder on HbA1c . levels

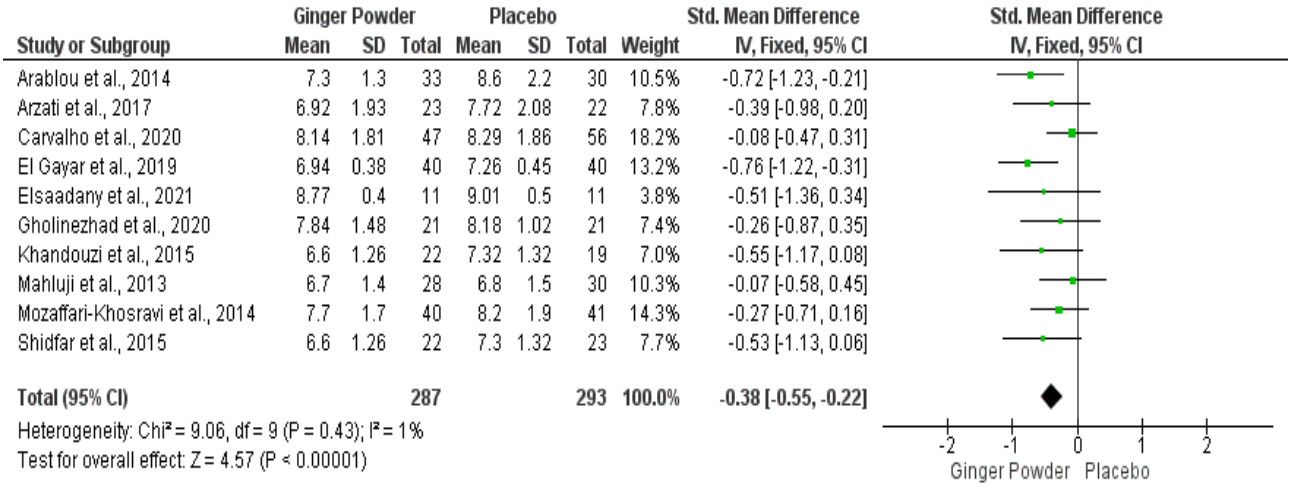

Figure 5. Forest plot of the effect of ginger powder on HbA1c in type 2 DM patients

Figure 5 shows that ginger powder is effective in reducing HbA1c levels in patients with type 2 diabetes. Type 2 DM patients who received ginger powder experienced a decrease in HbA1c levels 0.38 units lower than type 2 DM patients who received placebo and was statistically significant (Standardized Mean Difference= -0.38; 95% CI= -0.55 to -0.22; p<0.001). The heterogeneity of the research data shows I^2= 1% so that the distribution of the data is declared homogeneous (fixed effect model).

d. Funnel plot of Zingiber officinale powder on HbA1c levels

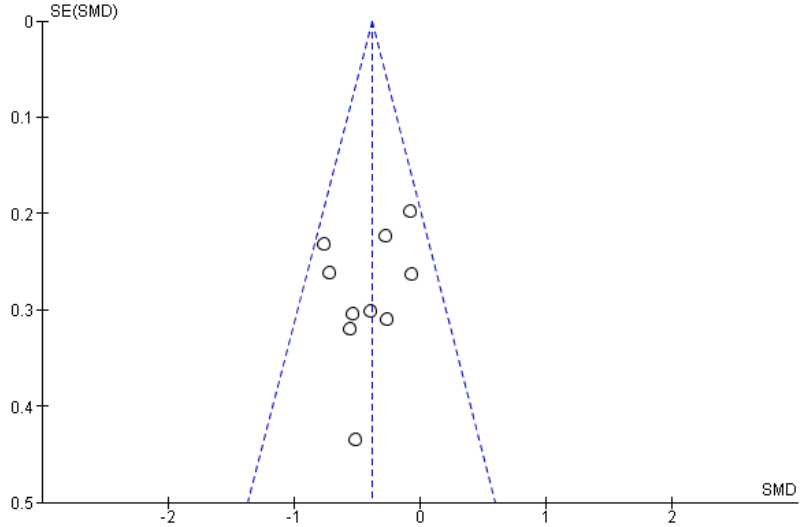

Figure 6. Funnel plot of the effect of ginger powder on HbA1c levels in type 2 DM patients

Based on Figure 6, there is a publication bias which is indicated by the asymmetry of the right and left plots, where there are 4 plots on the right and 5 plots on the left and there is 1 plot that touches the line. The plot on the right of the graph appears to have a standard error (SE) between 0.1 and 0.4. The plot on the left of the graph appears to have a standard error (SE) between 0.2 and 0.5.

DISCUSSION

Estimates of the combined effect of the effect of Zingiber officinale powder on patients with type 2 diabetes mellitus were processed using RevMan 5.3. The forest plot provides an overview of the information from each of the studies examined in the meta-analysis and estimates of the overall results. A funnel plot is a plot that depicts the approximate size of the effect of each study on an estimate of its accuracy which is usually standard error or standard error. (Murti, 2018).

The Effect of Zingiber officinale powder on GDP levels in type 2 DM patients

Based on the results of the analysis of 11 primary research articles, it showed that ginger powder was effective in reducing the GDP levels of type 2 DM patients. (Standardized Mean Difference = -0.79; 95% CI= -1.32 to -0.26; p=0.004). The heterogeneity of the research data shows I2 = 89% so that the distribution of the data is declared heterogeneous (random effect model). There are 3 primary studies that show significant value on the forest plot, which is indicated by not touching the horizontal line of each study with the vertical line on the forest plot, including the research of El Gayar et al. (2019), Elsaadany et al. (2021), and Rahimlou et al., (2019). The other eight studies even though showed insignificant results but the average GDP in the intervention group all decreased so that in total from the forest plot results there was a significant decrease in GDP levels in the intervention group compared to placebo. This significant value is influenced by several factors, including in all primary study groups the average value in the intervention group is smaller than the placebo group so that the cumulative SMD leads to intervention. The results of this study are in line with the research conducted by Ebrahimzadeh et al., (2022) which proved that the administration of ginger powder can reduce the GDP levels of type 2 DM patients. However, this study is not in line with the research conducted by Huang et al., (2019) which states that ginger powder has no significant effect on GDP levels in type 2 DM patients.

The results of this study are in line with the RCT research conducted by El Gayar et al., (2019), Rahimlou et al., (2019), and Shidfar et al., (2015) on type 2 DM patients who received ginger powder experienced a decrease in GDP. significantly compared to those receiving placebo. Another study by Ebrahimzadeh et al., (2022) also proved that the administration of ginger powder can reduce GDP levels in type 2 DM patients. However, this study is not in line with the RCT research conducted by Arablou et al., (2014), Arzati et al., (2017), Carvalho et al., (2020), Gholinezhad et al., (2020), Khandouzi et al., (2015), Mahluji et al., (2013), Mozaffari-Khosravi et al., (2014), and another study by Huang et al., (2019) which stated that ginger powder had no significant effect on GDP levels in type 2 DM patients.

The Effect of Zingiber officinale powder on HbA1c levels in type 2 DM patients

Based on the results of the analysis of 10 articles, it showed that ginger powder was effective in reducing HbA1c levels in type 2 DM patients. Type 2 DM patients who received ginger powder experienced a decrease in

HbA1c levels 0.38 units lower than those who received placebo and was statistically significant (Standardized Mean Difference = -0.38 ; 95% CI= -0.55 to -0.22; p<0.001). The heterogeneity of the research data shows I2 = 1% so that the distribution of the data is declared homogeneous (fixed effect model). There are 2 primary studies that show significant value in forest plots, namely Arablou et al., (2014) and El Gayar et al. (2019). The other eight studies even though showed insignificant results, but the average results of HbA1c levels in the intervention group all decreased so that in total from the forest plots there was a significant decrease in HbA1c levels in the intervention group compared to placebo. The results of this study are in line with research conducted by Ebrahimzadeh et al., (2022) and Huang et al., (2019) which proved that the administration of ginger powder can reduce HbA1c levels in type 2 DM patients. Ginger powder for 8-12 weeks in type 2 DM patients can reduce HbA1c levels compared to placebo.

The results of this study are in line with RCT studies conducted by El Gayar et al., (2019), Shidfar et al., (2015), Arablou et al., (2014), Gholinezhad et al., (2020), and other studies. by Ebrahimzadeh et al., (2022) and Huang et al., (2019) who proved that the administration of ginger powder can reduce HbA1c levels in type 2 DM patients. This provides stronger evidence that the administration of ginger powder for 8-12 weeks in Type 2 DM patients can lower HbA1c levels compared to placebo. But this study gives different results to the research conducted by Arzati et al., (2017), Carvalho et al., (2020), Khandouzi et al., (2015), Mahluji et al., (2013), and Mozaffari. -Khosravi et al., (2014) which stated that giving ginger powder to type 2 DM patients did not significantly affect HbA1c levels.

AUTHOR CONTRIBUTION

Fajar Novianto is the main researcher who selects topics, searches for, and collects research data. Didik Tamtomo and Hanung Prasetya played a role in analyzing data and reviewing research documents.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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