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Meta-Analysis

Effect of *Curcuma Longa* Rhizome Extract on Fasting Blood Sugar Levels and HbA1C in Type 2 Diabetes Mellitus: A Meta-Analysis

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ABSTRACT

Background: Diabetes mellitus (DM) is a metabolic disease that is developing into a serious global problem. Diabetes mellitus is characterized by an increase in blood levels that are more than the normal reference. In type 2 DM generally occurs due to reduced insulin secretion and sensitivity over time. Control of blood sugar levels can improve the patient's quality of life. This study aimed to analyze the effect of curcuma longa rhizome extract on fasting blood sugar levels and HbA1C in patients with type 2 diabetes.

Subjects and Method: This was a meta-analysis of a number of randomized controlled trials. The articles were obtained from PubMed, Google Scholar, Springerlink, BMJ, and Sciencedirect databases, published from 2010-2020. The article search was carried out by considering the eligibility criteria defined using the PICO model. P: Type 2 diabetes patients, I: Curcuma longa rhizome extract, C: Placebo, and O: Fasting blood sugar levels and HbA1C. The keywords to find articles are as follows: "Curcuma longa", OR "Curcumin" OR "Tumeric" OR "Curcuma" AND "Fasting blood glucose" AND "HbA1C" OR "Glicemic" OR "Diabetes Mellitus" AND "Randomized Controll Trials". Articles were collected using PRISMA flow diagrams. Articles were analyzed using the Review Manager 5.3 application.

Results: A total of 14 articles were reviewed in this study. Meta-analysis of 12 articles showed that the *curcuma longa* rhizome extract reduced fasting blood sugar levels (Standardized Mean Difference= -0.48; 95% CI= -0.61 to -0.34; p <0.001). The meta-analysis of 11 articles showed that administration of *curcuma longa* rhizome extract decreased HbA1C levels (Standardized Mean Difference= -0.40; 95% CI= -0.59 to -0.20; p <0.001). This meta-analysis combines primary studies from Iran, Japan, Thailand, China, Mexico, Brazil, and Australia

Conclusion: Curcuma longa rhizome extract reduces fasting blood sugar and HbA1C levels in patients with type 2 diabetes.

Keywords: Curcuma longa, Fasting blood sugar levels, HbA1C, diabetes mellitus type 2, randomized controlled trial

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BACKGROUND

Diabetes Mellitus (DM) is a group of metabolic diseases with characteristics including hyperglycemia that occurs due to insulin disorders, insulin work disorders, or a combination of the two (American Diabetes Association, 2019). Meanwhile, the 2017 International Diabetes Federation (IDF) predicts that there will be an increase in the number of DM sufferers in the world from 425 million in

2017 to 629 million in 2045 (IDF, 2017). Indonesia is in the 7th rank of the top 10 countries with the highest number of DM sufferers with a prevalence of 8.6% of the total population. This number is estimated to continue to increase from 8.4 million people in 2000 to around 21.3 million people in 2030 (Riskesdas, 2018).

Diabetes mellitus type 2 continues to develop due to the influence of cultural, economic, social, aging changes, diet such as increased consumption of processed foods and sweet drinks, reduced physical activity, unhealthy lifestyles, and behavior patterns. (WHO, 2019).

Complications that occur due to type 2 diabetes can include disorders of the blood vessels, both macrovascular (coronary heart disease, stroke, and peripheral vascular disease) and microvascular (retinopathy, neuropathy, and nephropathy). This disorder can occur in patients with type 2 diabetes who have long suffered from the disease or type 2 diabetes which has just been diagnosed (David, 2020). DM type 2 can be diagnosed through 4 criteria, namely checking fasting blood sugar levels, random blood sugar, HbA1C, and tests. Oral Glucose Tolerance (TTGO). (Perkeni, 2019).

The management of DM begins with implementing a healthy lifestyle (improved nutrition and physical activity) along with pharmacological interventions with oral anti-hyperglycemia drugs and / or injections. In addition to pharmacological therapy, there have been many studies related to the use of herbs which have been found to be used as alternative therapeutic options in type 2 DM patients, one of which is curcuma longa (Lim, 2016).

Curcuma longa in Indonesia itself is known as turmeric and has been used for generations as a traditional medicine. *Curcuma longa* is useful as an antioxidant, anti-inflammatory, antidiabetic, and immuno-modulatory, curcuma longa has also been shown to relieve diabetes symptoms and slow its development (Roxo et al., 2019). Several studies related to curcuma longa have proven that giving curcuma longa rhizome extract results in significant changes in blood sugar levels in type 2 DM patients (Shi et al., 2019).

Management of DM in general is to improve the patient's quality of life. In the short term, it aims to relieve complaints of DM symptoms and reduce the risk of acute complications. In the medium and long term, it is to prevent and inhibit the progression of complicating microangiopathies and macro-angiopathies. The ultimate goal of managing DM is to reduce morbidity and mortality. To achieve this goal, one of the steps is the need to control blood sugar levels (Perkeni, 2015).

This study aimed to examine the effect of curcuma longa rhizome extract on fasting blood sugar levels and HbA1C in type 2 DM.

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and meta-analysis. The articles used in this study were obtained from several databases including PubMed, Google Scholar, Springerlink, BMJ med and Sciencedirect. The keywords to find articles are as follows: "Curcuma longa", OR "Curcumin" OR "Tumeric" OR "Curcuma" AND "Fasting blood glucose" AND "HbA1C" OR "Glicemic" OR "Type 2 Diabetes Mellitus" AND "Randomized Controll Trials ".

2. Inclusion Criteria

The articles included in this study are full text with Randomized Controll Trials study and in English. The appropriate article should mention the population of type 2 DM patients, the intervention giving *Curcuma longa* rhizome extract and the outcume contained fasting blood sugar and HbA1C levels. Articles published in 2010-2020 with the results of the Mean Difference and Standard deviation.

3. Exclusion Criteria

The articles published in this study were articles with type 1 DM patients. The articles used an observational study design and used a sample of test animals. The comparison did

not use a placebo but used other herbal antidiabetic substances. There are other comorbidities.

4. Operational Definition of Variables

The article search was carried out by considering the eligibility criteria defined using the PICO model. The population in the study was type 2 DM patients with intervention in the form of giving curcuma longa rhizome extract. Meanwhile, the comparison is placebo and outcomes in the form of fasting blood sugar and HbA1C levels.

Curcuma longa rhizome extract which is processed in the form of capsules or other oral preparations. The measuring tool is a questionnaire.

Checking blood sugar levels is carried out after not consuming calories for at least 8 hours before the examination, the unit of measurement is in mg/dL, the measuring instrument is a spectrophotometer.

Laboratory tests of HbA1C levels in blood plasma with% HbA1C units, carried out at least 2 months after the intervention, the measuring instrument is a spectrophotometer.

5. Data Analysis

Data processing was carried out by the RevMan 5.3 by calculating the effect size and heterogeneity to determine which research models were combined and formed the final meta-analysis result.

RESULTS

The articles searched through a database with journals can be seen in Figure 1. Figure 2 shows the area of articles obtained from the continents of Asia, Australia, and America.

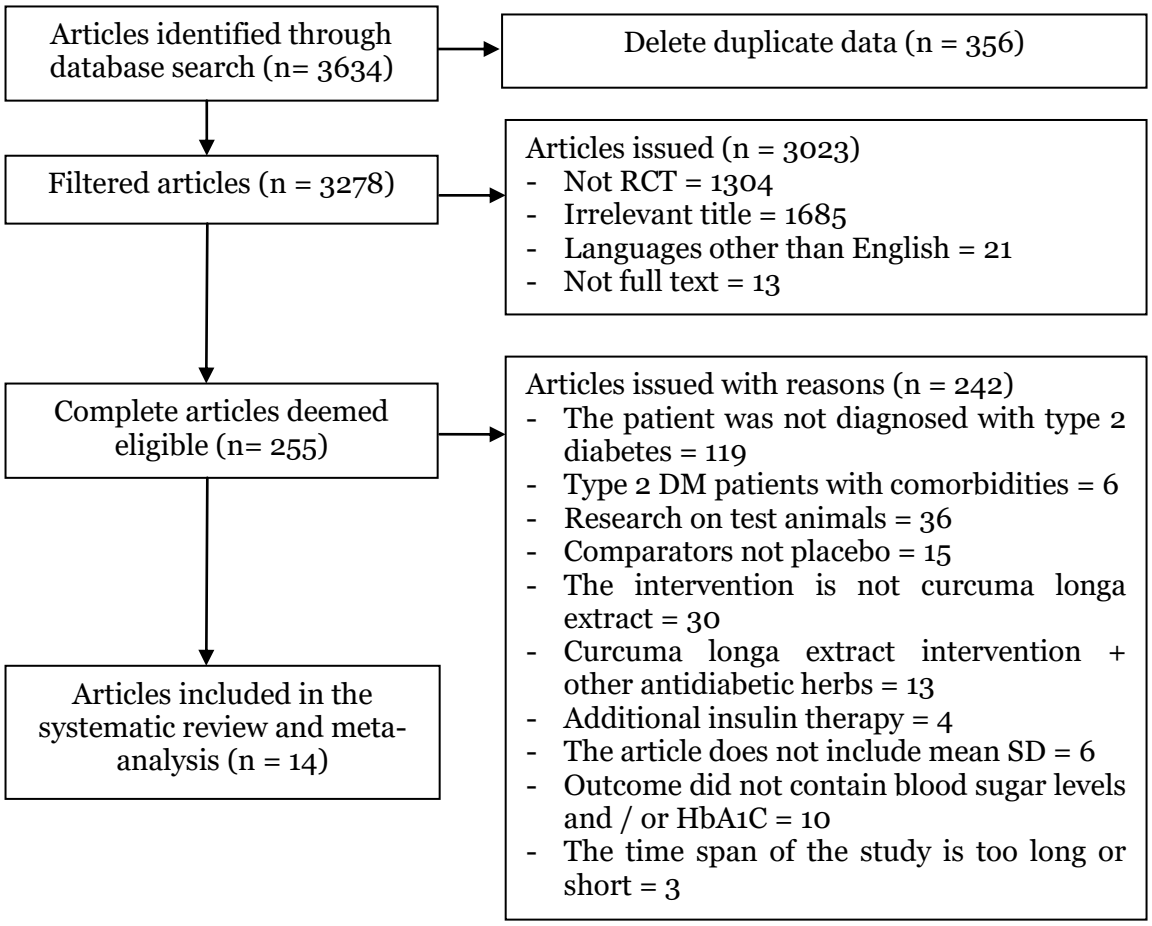

Figure 1. PRISMA flow diagram

Figure 2. Map of the research area of *Curcuma longa* rhizome extract on blood sugar levels in type 2 Diabetes Mellitus patients

The results of the quality assessment study on the effect of extra *Curcuma longa* rhizome on fasting blood sugar and HbA1C levels.

Table 1. Critical Appraisal Skills Checklist for RCT

Checklist	Adab et.al (2019)	Asadi et al (2019)	Alvarenga et al, (2020)	Chuengsamarn et al (2014)	Hodaei et al (2019)	Funamoto et al (2019)	Jimenez et al. (2015)	Mirzabeigi et at (2015)	Mokhtari et al (2020)	Na et al. (2012)	Panahi et al. (2017)	Rahimi et al. (2016)	Vanaie et al (2019)	Thota et al. (2019)
Does the research clearly address the focused statement / problem?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Is the Randomized Controlled Trial research method suitable for answering research questions?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are there enough subjects in the study to establish that the findings were not made by chance?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are subjects randomly allocated to the experimental and control groups? If not, could this be biased?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are inclusion / exclusion criteria used?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Were the two groups compa-	1	0	1	1	0	0	0	0	1	0	0	0	0	0

rable at study entry?														
Are objective and unbiased outcome criteria?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are objective and validated measurement methods used to measure the results? If not, were the results scored by some-one who did not know the group assignment (i.e. was the grading blended)?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Is the effect size practically relevant?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
How precise is the estimated effect. Are there any confidence intervals?	1	1	0	0	0	0	0	1	1	0	1	1	1	0
Could there be confounding factors that have not been taken into account?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the results applicable to your research?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total	12	11	11	11	10	10	10	11	12	10	11	11	11	10

Article Summary

The effect of curcuma longa rhizome extract on fasting blood sugar levels and HbA1c in patients with type 2 diabetes mellitus

Table 2. Descriptions of primary studies included in the meta-analysis

Author (year)	Titles	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Adab et al. (2019)	Effect of turmeric on glycemic status, lipid profile, hs-CRP, and total antioxidant capacity in hyper-lipidemic type 2 diabetes mellitus patients	Iran	RCT	I=39 C= 36	Pasien DM tipe 2	2100 mg esktrak curcuma longa perhari selama 10 minggu	Plasebo	GDP (mg/dL) I = 131.64 ± 28.33 C = 139.41 ± 41.57 HbA1C (%) I = 7.28 ± 1.59 C = 7.04 ± 0.98
Asadi et al.(2019)	Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus	Iran	RCT	I=40 C=40	Pasien DM tipe 2	240 mg nano-curcumin setara 1000 mg esktrak curcuma longaperhari selama 10 minggu	Plasebo	GDP (mg/dL) I = 165.7±52.3 C = 184.9±58.1 HbA1C (%) I = 8.18±1.96 C = 9.22±1.72
Alvarenga et al. (2020)	Impact of curcumin supplementation on expression of inflammatory transcription factors in hemodialysis patients	Brazil	RCT	I= 14 C= 14	Pasien DM tipe 2 Nefropati	2500 mg ekstrak curcuma longaper hari selama 12 minggu	Plasebo	GDP (mg/dL) I= 139.0 ± 58.2 C= 106.8 ± 32.5 HbA1C (%) I = 6.8 ± 1.0 C = 6.3 ± 0.9
Chuengsamarn et al.(2012)	Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract	Thailand	RCT	I= 107 C= 106	Pasien DM tipe 2	1500 mg ekstrak curcuma longaper hari selama 12 minggu	Plasebo	GDP (mg/dL) I= 123.2 ± 25 HbA1C (%) I = 6.5±0.9 C = 7±1.1 C= 139.3 ± 35.9
Funamoto et al. (2019)	Effects of Highly Absorbable Curcumin in Patients with Impaired Glucose Tolerance and Non-Insulin-Dependent Diabetes Mellitus	Japan	RCT	I=15 C=18	Pasien DM tipe 2	180 mg nano-curcumin setara 750 mg ekstrak curcuma longa/hari selama 12 minggu	Plasebo	HbA1C (%) I = 6.2±0.5 C = 6.5±0.3

Author (year)	Titles	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Hodaeiet al. (2019)	The efect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes	Iran	RCT	I=21 C=23	Pasien DM tipe 2	1500 mg ekstrak curcuma longa per hari selama 10 minggu	Plasebo	GDP (mg/dL) I = 153±33 C = 147±40.4 HbA1C (%) I = 11±2 C = 11.1±1.
Mirzabeigi et al. (2015)	The Effect of Curcumin on some of Traditional and Non-traditional Cardiovascular Risk Factors Randomized, Double-blind, Placebo-controlled	Iran	RCT	I= 17 C= 16	Type 2 DM patients	1500 mg of curcuma longa extract per day for 10 weeks	Placebo	GDP (mg/dL) I= 122.50 ± 35.68 C=116.46 ± 24.96
Mokhtari et al. (2020)	The effects of curcumin intake on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled	Iran	RCT	I= 25 C= 25	Type 2 DM patients	80 mg of nanocurcumin equivalent to 325 mg of curcuma longa extract per day for 12 weeks	Placebo	GDP (mg/dL) I= 136.1 ± 32.5 C=148.0 ± 45.0 HbA1C (%) I = 8.3±2.2 C = 8.1±1.7
Na et al. (2012)	Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial	China	RCT	I= 50 C=50	Type 2 DM patients	300 mg of curcuma longa extract per day for 12 weeks	Placebo	GDP (mg/dL) I= 131±31.9 C= 147.1±37.1 HbA1C (%) I = 7±2 C = 8±2.9
Jimenez at al. (2012)	The effect of dietary supplementation with curcumin on redox status and Nrf2 activation in patients with nondiabetic or diabetic proteinuric	Mexico	RCT	I=28 C=23	Nephropathy type 2 DM patients	320 mg of curcuma longa extract per day for 10 weeks	Placebo	GDP (mg/dL) I= 120.9±8.8 C= 122.6 ±11.7
Panahiet al (2017)	Effects of Curcuminoids Plus Piperine on Glycemic, Hepatic and Inflammatory Biomarkers in Patients with Type 2 Diabetes Mellitus	Iran	RCT	I=50 C=50	Type 2 DM patients	500 mg of curcuma longa extract per day for 12 weeks	Placebo	GDP (mg/dL) I = 154 ± 34 C = 171 ± 26 HbA1C (%) I = 6.5±1 C = 7.3±0.8
Rahimi et al (2016)	The effect of nano-curcumin on HbA1c, fasting blood glucose, and	Iran	RCT	I=35 C=35	Type 2 DM patients	80 mg nano-curcumin	Placebo	GDP (mg/dL) I = 120.29±38.01

Author (year)	Titles	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
	lipid profile in diabetic subjects: a randomized clinical trial					equivalent to 325 mg of curcuma longa extract per day for 12 weeks		C = 176.0±61.56 HbA1C (%) I = 7.31±1.54 C = 9±2.33
Thota et al (2020)	Curcumin and omega-3 polyunsaturated fatty acids supplementation reduces insulin resistance and blood lipids individuals with high risk of type 2 DM	Australia	RCT	I= 15 C= 16	Type 2 DM patients	1000 mg of curcuma longa extract per day for 12 weeks	Placebo	HbA1C (%) I = 6.5±0.7 C = 7±0.6
Vanaie et al (2020)	Curcumin as a major active component of turmeric attenuates proteinuria in patients with overt diabetic nephropathy	Iran	RCT	I=27 C= 19	Nephropathy type 2 DM patients	1500 mg of curcuma longa extract per day for 10 weeks	Placebo	GDP (mg/dL) I= 186.92±81.30 C= 214.05±93.64

a. Forest Plot of *Curcuma longa* on fasting blood sugar levels

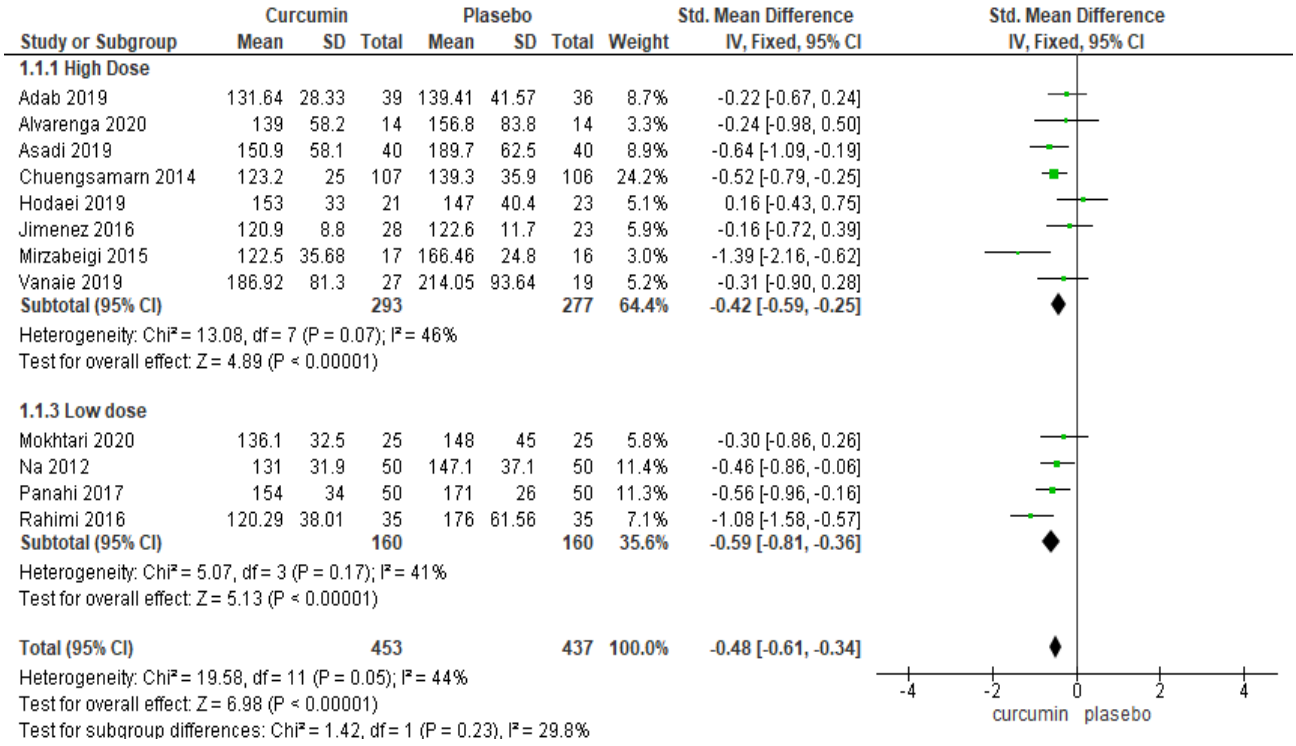

Figure 3. Forest plot of the effect of curcuma longa rhizome extract on reducing fasting blood sugar levels

b. Funnel plot of *Curcuma longa* on fasting blood sugar levels

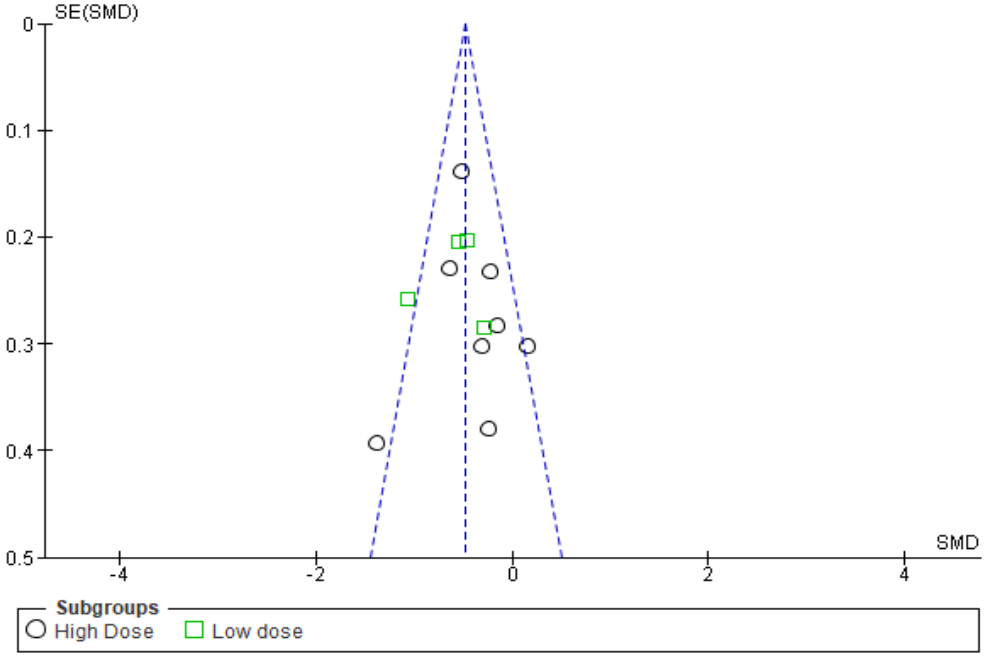

Figure 4. Funnel plot of the effect of curcuma longa rhizome extract on reducing fasting blood sugar levels

The results of the meta-analysis are seen in Figure 3. For high and low doses, giving curcuma long extract reduced fasting blood sugar levels by 0.48 compared to placebo and it was statistically significant. The heterogeneity of the research data showed I^2= 44% so that the distribution of the data was stated as homogeneous. Sub-group analysis at high doses could reduce fasting blood sugar levels by 0.42 compared to placebo. Whereas subgroup analysis at low doses can reduce fasting blood sugar levels by 0.59 compared to placebo or greater than high doses.

Based on the funnel plot of Figure 4, the overall data from high doses and low doses shows bias because there are more plots on the right. The high dose subgroup showed a publication bias which was characterized by asymmetry of the right and left plots where 4 plots were on the right, 2 plots were on the left and 1 plot touched the line. Meanwhile, the low dose subgroup showed no publication bias which was indicated by the symmetrical plot of the right and left where 1 plot was on the right, 1 plot was on the left and 2 plots touched the line. The plot on the left of the graph appears to have a standard error between 0.1 and 0.4 and the plot is on the right. Based on the funnel plot of Figure 4, the overall data from high dose and low dose shows bias because there are more plots on the right. The high dose subgroup showed a publication bias which was characterized by asymmetry of the right and left plots where 4 plots were on the right, 2 plots were on the left and 1 plot touched the line. Meanwhile, the low-dose subgroup showed no publication bias which was indicated by the symmetrical plot of the right and left where 1 plot was on the right, 1 plot was on the left and 2 plots touched the line. The plot on the left of the graph appears to have a standard error between 0.1 and 0.4 and the plot is on the right.

c. Forest Plot of *Curcuma longa* on HbA1C levels

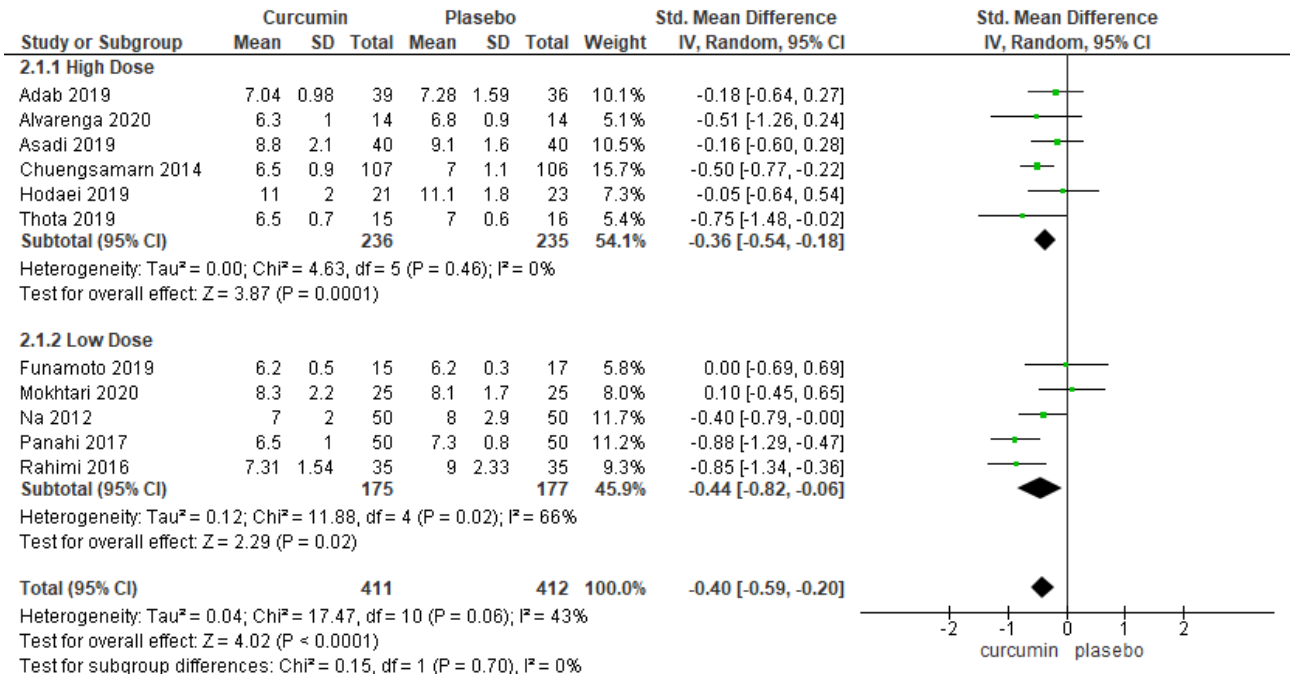

Figure 5. Forest plot of the effect of *Curcuma longa* rhizome extract on HbA1C levels

c. Funnel plot of *Curcuma longa* on HbA1C levels

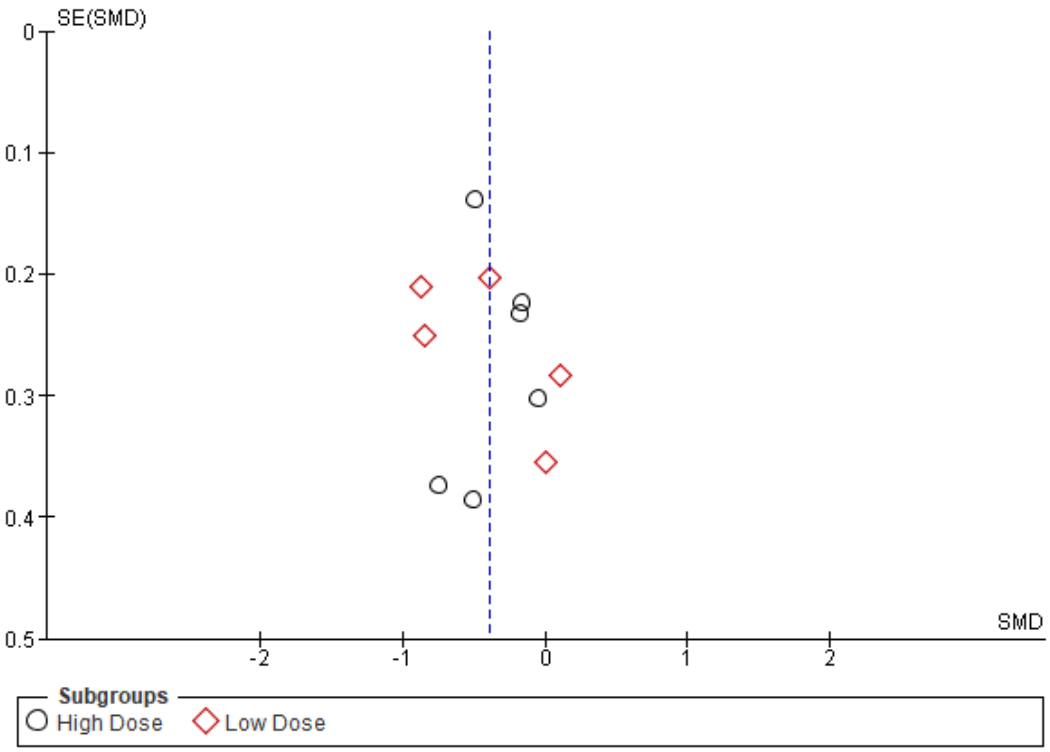

Figure 6. Funnel plot of the effect of *Curcuma longa* rhizome extract on reducing HbA1C levels

The results of the meta-analysis seen in Figure 5 for the overall dose decreased HbA1C levels by 0.44 compared to placebo and were statistically significant. The overall heterogeneity of the data I^2 = 43% or homogeneous but in the low dose subgroup I^2= 66% or heterogeneous. The high-dose subgroup analysis reduced HbA1C by 0.36 compared to placebo and was statistically significant. Subgroup analysis regarding low doses in type 2 DM patients reduced fasting blood sugar levels by 0.44 compared to placebo and was statistically significant and not statistically significant.

Based on the funnel plot of Figure 6, the high-dose subgroup shows no publication bias which is indicated by symmetrical plots on the right and left, where 3 plots are on the right, 3 plots are on the left. Meanwhile, the low dose subgroup showed no publication bias, which was indicated by a symmetrical plot on the right and left, where 2 plots were on the right, 2 plots on the left and 1 plot touched the line. The plot on the left of the graph appears to have a standard error between 0.1 and 0.4 and the plot on the right has a standard error between 0.2 and 0.4.

DISCUSSION

Diabetes mellitus is a metabolic disease characterized by hyperglycemia. Diabetes mellitus is currently the number one non-communicable disease and the number four or five cause of death in various countries (WHO, 2019). Diabetes Mellitus Type 2 generally occurs due to conditions of insulin resistance and or reduced insulin secretion. This will cause symptoms in the form of polyuria, polydipsia and polyphagia. Diabetes Mellitus conditions that are not treated with controlled therapy can

increase the risk of macrovacular and microvascular complications. One of the parameters that need to be considered in diabetes mellitus therapy is blood glucose parameters. In the blood glucose parameters that are commonly used are fasting blood sugar and HbA1C parameters (Nam et al, 2017).

Effect of Curcuma Longa rhizome extract on reducing fasting blood sugar levels

There are 12 research articles Randomized Controlled Trial as a source of meta-analysis of the effect of curcuma longa rhizome extract on fasting blood sugar levels. The analysis was carried out with the review manager 5.4 application, the results were interpreted in the form of a forest plot and a funnel plot.

The results of the meta-analysis of the RCT study showed that giving curcuma longa rhizome extract reduced the effect size of 0.48 compared to placebo on fasting blood sugar levels and was statistically significant (SMD-0.48, 95% CI -0.61, -0.34, p<0.001). The heterogeneity of the research data shows I^2= 44% so that the distribution of the data is declared homogeneous (fixed effect model).

The results in the high-dose subgroup analysis showed a decrease of 0.42 and were statistically significant (SMD-0.42, 95% CI -0.59, -0.25, p <0.001). The results of this study are in line with Chuengsamarn et al (2014) which involved 213 patients with type 2 diabetes. for three months showed that patients receiving curcuma long rhizome extract supplements at high doses had lower fasting blood sugar levels than those receiving placebo (SMD -0.52, 95% CI -0.79, -0.25).

The results in the low dose subgroup analysis showed a decrease of 0.59 and were statistically significant (SMD-0.59, 95% CI -0.81, -0.36, p <0.001). The results of this study are in line with the study by Panahiet al (2017) which involved 100 patients. Type 2 diabetes mellitus for three months showed that patients who received curcuma long rhizome extract supplements at low doses had lower fasting blood sugar levels than those receiving placebo (SMD -0.56, 95% CI -0.96, -0.16).

Effect of Curcuma Longa rhizome extract on reducing HbA1C levels

There are 11 research articles with the Randomized Controlled Trial study design as a meta-analysis source of the effect of curcuma longa rhizome extract on HbA1C levels. The analysis was carried out with the review manager 5.4 application, the results were interpreted in the form of a forest plot and a funnel plot.

The results of the meta-analysis of the RCT study showed that giving curcuma longa rhizome extract reduced the effect size by 0.40 compared to placebo on HbA1C levels and was statistically significant (SMD= -0.40, 95% CI= -0.59, -0.20, p <0.001). The heterogeneity of the research data showed I^2= 43%.

The results on the high dose subgroup analysis showed a reduction of 0.36 and were statistically significant (SMD-0.36, 95% CI -0.54, -0.18, p <0.001). The results of this study are in line with the study by Chuengsamarnet al (2014) which involved 213 type 2 DM patients for three months showing that patients who received high doses of curcuma long rhizome extract supplements experienced lower levels of HbA1C than receiving placebo (SMD -0.50, CI 95% -0.77, -0.22).

The results on the low dose subgroup analysis showed a reduction of 0.44 and were statistically significant (SMD-0.44, 95% CI -0.82, -0.06, p <0.001). The results of this study are in line with a study by Panahiet al (2017) involving 100 type 2 DM patients for three months showing that

patients who received curcuma longa rhizome extract supplements at low doses experienced a decrease in fasting blood sugar levels than those who received placebo (SMD -0.88, CI 95 % -1.29, -0.47).

The dosage of curcuma longa rhizome extract ranges from 300 mg / day to 2100 mg/day. For high doses it has a range above 1000 mg/day. For low doses it has a range below 1000 mg / day.

From the subgroup analysis of high and low doses, the administration of *Curcuma longa* rhizome extract at low doses had a greater effect on the decrease compared to high doses. Because the dosage effectiveness test (ED50) of rinpang curcuma longa extract on fasting blood sugar and HbA1C levels has not been found, there are no reinforcing data to conclude that the appropriate dose is used in reducing fasting blood sugar and HbA1C levels.

The fall in blood sugar levels is influenced by increased insulin secretion and increased insulin sensitivity. It occurs because the active ingredient curcuminoid in curcuma longa functions to repair pancreatic β cells and stimulate increased insulin secretion. The effect of increasing insulin sensitivity can also occur due to the influence of curcuminoids.

AUTHOR CONTRIBUTION

This study is self-funded.

CONFLICT OF INTEREST

Riska is the main researcher who selects the topic, explores and collects research data. Didik and Hanung played a role in analyzing data and reviewing research documents.

FUNDING AND SPONSORSHIP

There is no conflict of interest in this study.

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