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Meta-analysis

Effect of Garlic Powder Supplementation on Total Cholesterol and Low Density Lipoprotein Level in Patient with Hypercholesterolemia: A Meta-Analysis

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ABSTRACT

Background: Hypercholesterolemia is a risk factor for cardiovascular disease that can cause death and disability, so it must be managed properly. Garlic flour (GP) is one of the dosage forms of garlic that has the potential to reduce cholesterol. This study is a systematic review and meta-analysis that aims to determine the effectiveness of GP in reducing total cholesterol (TC) and low density lipoprotein (LDL).
Subjects and Method: Search articles through the Pubmed database, Google scholar, Proquest, Springer link, and Science direct with the appropriate keywords. Population= patients with hypercholesterolemia. Intervention= GP. Comparison= placebo. Outcome= TC and LDL. Inclusion criteria included complete articles in English or Indonesian published from 2010-2022, Randomized Controlled Trial (RCT) design, subjects >18 years old with hypercholesterolemia, the study had a complete fat profile outcome, duration of intervention 2 weeks-12 months. The flow of article selection is based on the PRISMA flow diagram. Meta-analysis using RevMan 5.3 with effect size standardized mean difference (SMD) and Random Effect Model (REM) analysis model.
Results: A total of 10 articles were eligible for a meta-analysis. The GP group had TC levels 1.49 units lower than the placebo group (SMD = -1.49; 95% CI = -1.95 to -0.55; p = 0.005) and LDL levels 0.68 units lower than the placebo group (SMD= -0.68; CI95). %= -1.08 to -0.27; p=0.001). Subgroup analysis based on the length of the intervention showed that administration of GP <12 weeks only significantly reduced TC while administration > 12 weeks significantly reduced TC and LDL.
Conclusion: GP is effective in lowering TC and LDL especially at 12 weeks or more.

Keywords: garlic powder, hypercholesterolemia, RCT

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BACKGROUND

Hypercholesterolemia is a risk factor for cardiovascular disease (Zarate et al., 2016; WHO, 2022). Based on data from the World Health Organization (WHO) (2022) increased cholesterol levels are responsible for one third of ischemic stroke cases and are estimated to cause 2.6 million deaths in the world. Elevated cholesterol levels also accounted for 29.7 million (2%) of the number of cases of global Disability Adjusted Life Years (DALYs). The prevalence of increased total cholesterol levels in the world's population aged 18 years and over in 2008 reached 39% (WHO, 2022). In Indonesia, from the 2018 Basic Health

Research (RISKEDAS) data, it is known that the proportion of the population aged > 15 years who experienced an increase in total cholesterol (> 200 mg/dl) was quite high at 48.8% and low density lipoprotein (LDL) levels (>130 mg/dl) 37.3% (Agency for Health Research and Development, 2019).

Currently, statins are the most widely used cholesterol-lowering drug class in the world (Ward et al., 2019). Statins have been marketed since approximately 30 years ago and have a fairly good effectiveness in reducing LDL levels as the main target of hypercholesterolemia therapy with a reduction of between 20-55% (Ward et al., 2019; Galicia-garcia et al., 2020). Statins have also been reported to reduce the risk of cardiovascular events in dyslipidemic patients (Hadjiphilippou and Ray, 2019; Ward et al., 2019; Galicia-garcia et al., 2020). Unfortunately, statins have some potential side effects, such as striated muscle pain (1-10%), striated muscle damage/rhabdomyolysis (0.1%), liver damage (1%), kidney disorders, neurological disorders, increased risk of diabetes mellitus (10-20%), impaired heart muscle contractility and in some cases can trigger autoimmune diseases (Ramkumar et al., 2016; Nazir et al., 2017; Newman et al., 2019; Ward et al., 2019; Galicia). -garcia et al., 2020). Bradley et al. (2019) reported that more than 25% of dyslipidemic patients who were actually eligible for therapy with statins were not on the therapy because the doctor did not prescribe it or the patient refused or did not want to continue taking it.

Herbal supplementation can be an alternative therapy for dyslipidemia, namely in borderline and mild conditions. The use of herbs is considered safer and has fewer side effects (Hasani-ranjbar et al., 2010; Bahmani et al., 2015). One of the herbs that has been widely studied is garlic. Garlic has long been used traditionally to improve cardiovascular health. Garlic powder (GP) is one of the most widely sold dosage forms as supplements and researched (Lawson and Hunsaker, 2018; Subramanian et al., 2020).

The results of previous studies showed an inconsistency in the efficacy of GP supplementation on dyslipidemia. Several studies stated that garlic flour was not efficacious in improving the fat profile, while several other studies stated the opposite (Ried et al., 2013; Lawson and Hunsaker, 2018). The meta-analysis method, namely statistical analysis of a combination of several different studies with the same research design and type, can be used to overcome this problem (Altman et al., 2022). This study is the latest meta-analysis to determine the effect of GP supplementation on the fat profile of patients with hypercholesterolemia, focusing on primary articles published from 2010-2022.

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and meta-analysis. Data comes from primary studies in the form of articles published online in several scientific journals. Search articles through the Pubmed database, Google scholar, Proquest, Springer link, and Science direct. Keywords used “garlic” OR “garlic extract” OR “garlic powder” OR “allicin” OR “Allium sativum” AND “lipid profile” OR “cholesterol” OR “LDL” AND “hypercholesterolemia” OR “dyslipidemia” OR “hyperlipidemia ” AND “placebo” AND “RCT” OR “Randomized Controlled Trial”.

The flow of article selection was systematic using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) from Cochrane. The primary study quality assessment used critical appraisal tools for Randomized Controlled Trials (RCT) which was adapted from the Critical Appraisal of a Controlled Study published by

the Center for Evidence-Based Management (CEBMa) University of OXFORD in 2014.

2. Inclusion Criteria

The criteria that must exist in the primary article are complete articles in English or Indonesian, Randomized Controlled Trial (RCT) design, subjects >18 years old, both male and female, who suffer from hypercholesterolemia (TC levels> 200 mg/dl or LDL levels > 100 mg/dl), GP intervention in the form of tablets, capsules or flour with a comparison of placebo or without treatment, the study outcome contains complete data on levels of the four fat profiles (TC, LDL, Triglycerides/TG, and High density lipoprotein/HDL) before and after the intervention, the length of the intervention between 2 weeks – 12 months.

3. Exclusion Criteria

Articles were excluded from the study if they had a design other than RCT, intervention of garlic flour in combination with other medicinal plants or other cholesterol-lowering agents, studies prior to 2010.

4. Operational Definition of Variables

Garlic flour was defined as fresh garlic which was dried at a low temperature (<600C) and then mashed to form flour with the main active ingredient being allicin. Garlic flour supplementation is defined as the oral administration of garlic powder at a specific dose in milligrams or grams.

TC and LDL levels are total cholesterol and low density lipoprotein levels in the blood which are determined by taking a sample of the subject's blood and then examined by certain methods in the laboratory. The units for TC and LDL in this study were mg/dl. The mmol/L unit will be converted to mg/dl with a multiplier of 38.67.

Hypercholesterolemia in this study was defined as a condition in which blood TC levels > 200 mg/dl or LDL levels in blood > 100 mg/dl. The selection of the primary study was based on the eligibility criteria using the Population, Intervention, Comparison/Control, Outcome (PICO) model. The population in this study were patients with hypercholesterolemia, intervention of garlic flour (GP), comparison of placebo/without treatment and the outcome of TC and LDL levels in the blood.

5. Data Analysis

Data analysis was performed using Rev.Man 5.3 with continuous outcome data type. The effect size uses the Standardized Mean Difference (SMD). Rev.Man 5.3 will calculate the effect size and heterogeneity that is combined from all primary studies to form the final results of the meta-analysis.

RESULTS

The search process and article selection flow are shown in Figure 1. Ten articles that met the criteria came from the European continent (2 articles) and the Asian continent (8 articles).

The critical appraisal score can be seen in table 1 while information about each primary study is presented in table 2. Table 1, researchers conducted an assessment of the quality of the study used Critical Appraisal Skill Programme (CASP) for RCT checklist (CASP, 2021):

a. Did the experiment answer the clinical problem clearly?
b. Is the intervention given to the patient randomized?
c. Are patients, health workers, and researchers blinded?
d. Are the study groups similar at the start of the study?
e. Outside of the intervention studied, were the study groups treated equally?
f. Are all patients included in the study properly accounted for in the conclusions? Were all patients analyzed according to the randomized study groups?

g. Is the effect of the intervention large enough?
h. What is the precision of the estimated effect of the intervention?
i. Are the results applicable to the context of practice or local populations?
j. Are all other clinically important outcomes considered in this article?
k. Do the benefits provided by the intervention outweigh the costs and disadvantages?

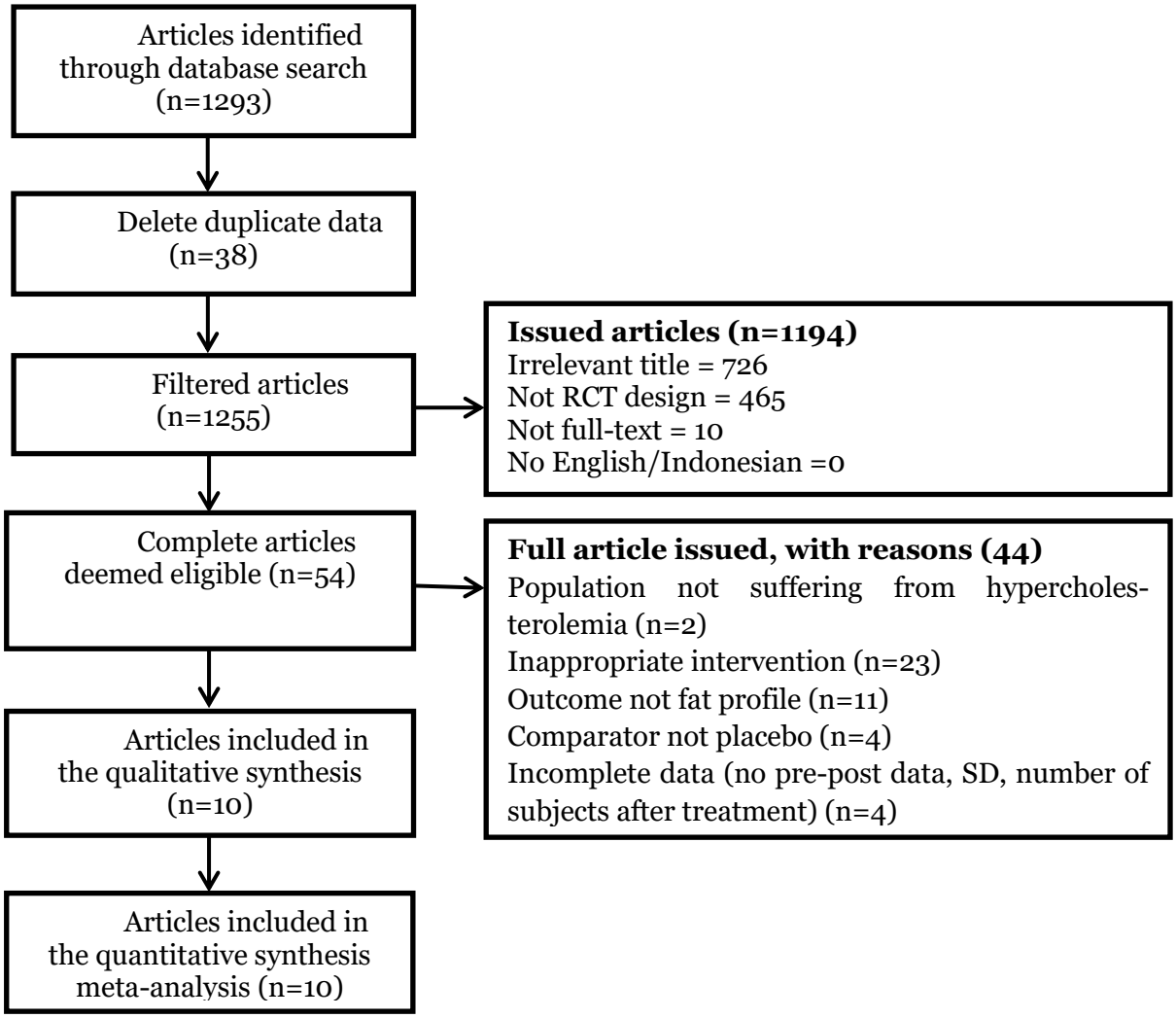

Figure 1. Research process flow with PRISMA flow diagram

Table 1. Description of the primary studies included in the meta-analysis of the effect of GP supplementation on the fat profile of patients with hypercholesterolemia.

Author and year	Place	Study Design	Sample	Population	Intervention	Comparison	Outcome
Sobenin et al. (2010)	Rusia	RCT	I :26 C: 25	Hypercholesterolemic patients with coronary heart disease	Slow-release GP tablets (Allicor) 150 mg 2x1 (300mg/ day) for 12 months	Plasebo	TC, LDL, TG dan HDL
Szulinska et al. (2018)	Polandia		I :46 C: 46	Hypercholesterolemic and obese patients	GP Capsules (Garlicin) 200 mg 2x1 (400mg/day) for 12 weeks Metformin	Plasebo	TC, LDL, TG dan HDL
Kumar et al. (2013)	India	RCT	I :30 C: 30	Hypercholesterolemic, DM and Obese patients	GP capsules (Lasuna) 250 mg 2x1 daily (500mg/day) for 12 weeks	Metformin	TC, LDL, TG dan HDL
Mariam and Devi (2020)	India	RCT	I a: 60 C : 60	Menopausal women with hyperlipidemia	GP capsules 500 mg 2x1 (1000 mg/day) for 12 weeks	No intervention	TC, LDL, TG dan HDL
Sangouni et al. (2020)	Iran	RCT	I :45 C: 43	Patients with hypercholesterolemia and fatty liver grade 1-3	GP film-coated tablets 400 mg 4x1 (1600 mg/day) for 12 weeks	Placebo	**a.6th week** TC, LDL, TG and HDL **b. 12th week** TC, LDL, TG, and HDL
Soleimani et al. (2020)	Iran	RCT	I :47 C: 51	Patients with non-alcoholic hypercholesterolemia and hepatic steatosis	GP film-coated tablets 400 mg 2x1 (800mg/day) for 15 weeks.	Placebo	TC, LDL, TG, and HDL
Alami-Harandi et al. (2015)	Iran	RCT	I :22 C: 22	Primigravida pregnant women with hypercholesterolemia and risk of pre-eclampsia	GP tablets 400 mg 1x1 daily for 9 weeks	Placebo	TC, LDL, TG, and HDL
Jawad et al. (2018)	Irak	RCT	I :6 C: 6	Patients with hypercholesterolemia and essential hypertension	Ramipril 5g 1x1 GP Tablet 400 mg 1-1-1/2 (1000 mg) daily for 4 weeks	Ramipril 5g 1x1	**a.2nd weeks** TC, LDL, TG, HDL **b. 4th week** TC, LDL, TG, and HDL
Zeb et al. (2018)	Pakistan	RCT	I :20 C:20	Patients with hyperlipidemia	GP 2000mg per day for 40 days	-	**a. 20th days** TC, LDL, TG and HDL **b. 40th days** TC, LDL, TG, and HDL
Limbu *et al.* (2019)	Nepal	RCT	I :56 C: 56	Dyslipidemic patients	GP capsules (Lasuna) 250mg 1x1 daily for 90 days	Placebo	TC, LDL, TG, and HDL

Table 1. Assessment of article quality using Critical appraisal tools for Randomized Controlled Trials (RCT)

Primary Study	Criteria											Total
	1	2	3	4	5	6	7	8	9	10	11	
Alami-Harandi *et al.* (2014)	1	1	0	0	1	1	0	0	1	1	1	7
Jawad *et al.* (2018)	1	1	0	0	1	1	0	0	1	1	1	7
Kumar *et al.* (2013)	1	1	0	1	1	1	1	0	1	1	1	9
Limbu *et al.* (2019)	1	1	0	1	1	1	1	0	1	1	1	9
Mariam and Devi (2020)	1	1	0	1	1	1	1	0	1	1	1	9
Sangouni *et al.* (2020)	1	1	1	1	1	1	1	0	1	1	1	10
Sobenin *et al.* (2010)	1	1	1	1	1	1	1	0	1	1	1	10
Soleimani *et al.* (2020)	1	1	1	1	1	1	1	0	1	1	1	10
Szulinska *et al.* (2018)	1	1	1	0	1	1	1	0	1	1	1	9
Zeb *et al.* (2018)	1	1	0	0	1	1	1	0	1	1	1	7

Note: Score 1= Yes, Score 0= Can't tell

1. Total Cholesterol (TC)

The first outcome is TC levels with the results of the meta-analysis presented in the form of forest plots and funnel plots.

a. Forest plot

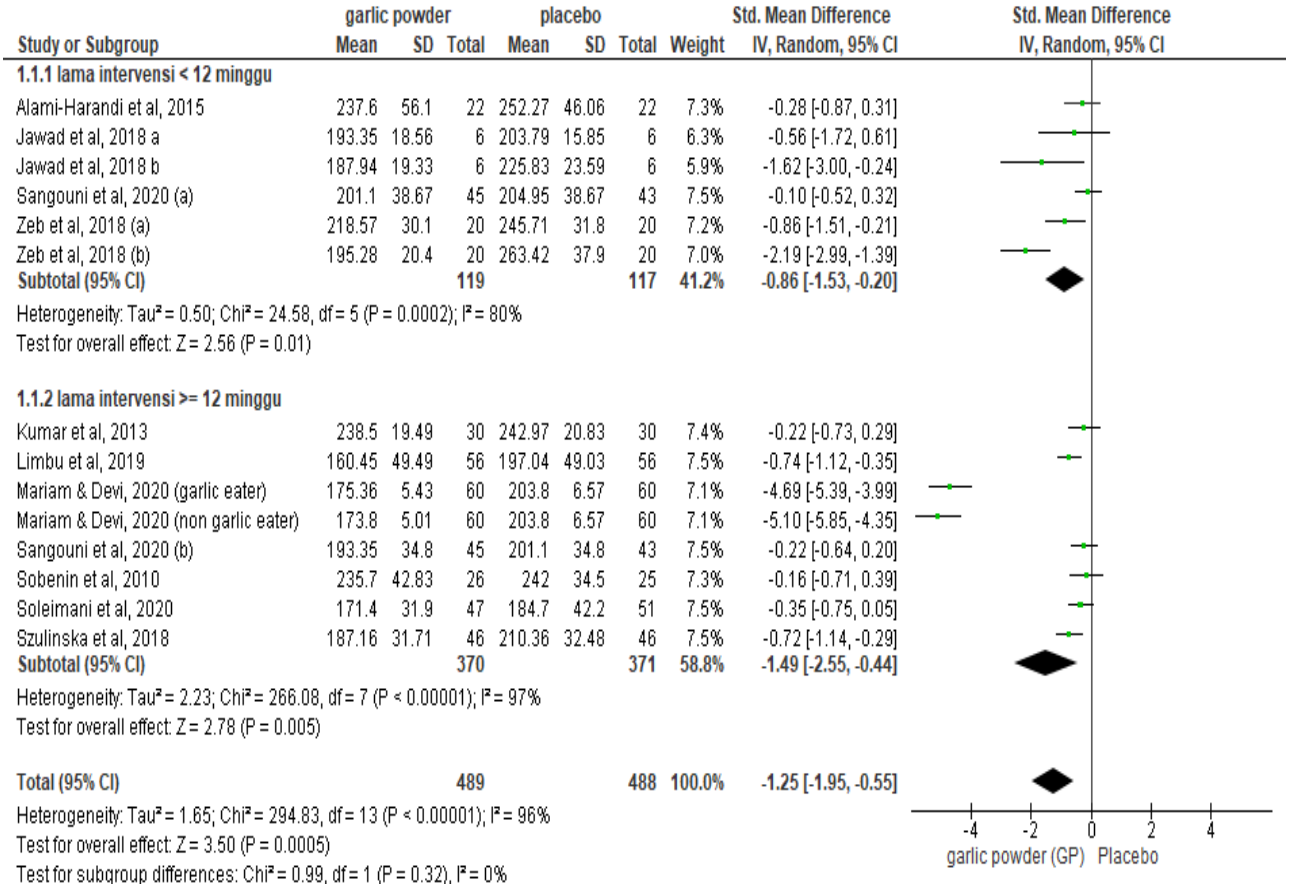

Figure 2. Forest plot meta-analysis of the effect of GP supplementation on TC levels in patients with hypercholesterolemia

The forest plot in Figure 2 shows that GP supplementation was effective in lowering total cholesterol levels in patients with hypercholesterolemia. The group given GP supplementation had a total cholesterol level of 1.25 units lower than the placebo group (Standardized Mean difference=-1.25; 95% CI= -1.95 to -0.55; p<0.001). The effectiveness of this GP was also seen in the subgroup with intervention duration < 12 weeks (Standardized Mean Difference=-0.86; 95% CI= -1.53 to -0.20; p=0.010) and intervention duration > 12 weeks (-1.49; 95% CI= -2.55 to -0.44; p=0.005). There was high heterogeneity between studies (I^2=96%; p=<0.001). The analytical model used is the Random Effect Model (REM) (Figure 3).

b. Funnel plot

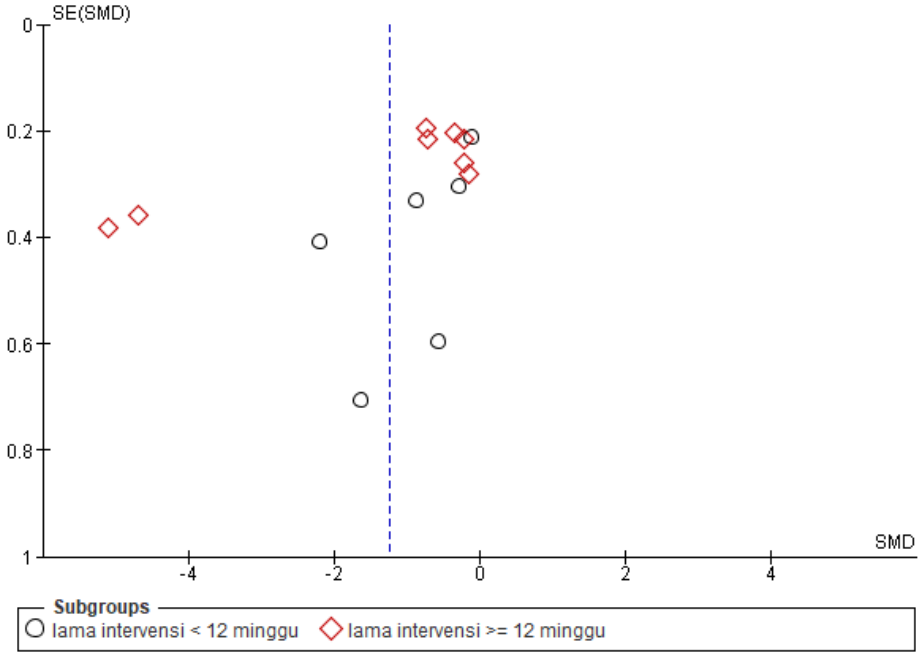

Figure 3. Funnel plot meta-analysis of the effect of GP supplementation on TC levels in patients with hypercholesterolemia

The funnel plot in Figure 3 shows no publication bias. In the primary study with a small sample size, the distribution of estimates is symmetrical between the right and left of the mean line.

2. Low Density Lipoprotein (LDL)

a. Forest plot

The forest plot in Figure 4 shows that garlic flour supplementation was effective in lowering LDL levels in patients with hypercholesterolemia. The group receiving GP supplementation had LDL levels 0.68 units lower than the placebo group (Standardized Mean difference=-0.68; 95% CI= -1.08 to -0.27; p= 0.001). Analysis by subgroup showed that GP supplementation with an intervention duration of <12 weeks was not significant in reducing LDL levels (Standardized Mean difference=-0.55; 95% CI= -1.30 to 0.21; p=0.15), while the intervention duration >12 weeks, was significant in reducing blood levels. LDL (Standardized Mean difference=-0.77; 95% CI= -1.25 to -0.28; p=0.002). Heterogeneity between studies was high (I^2=88%; p<0.001). The analytical model used is the Random Effect Model (REM) (Figure 5).

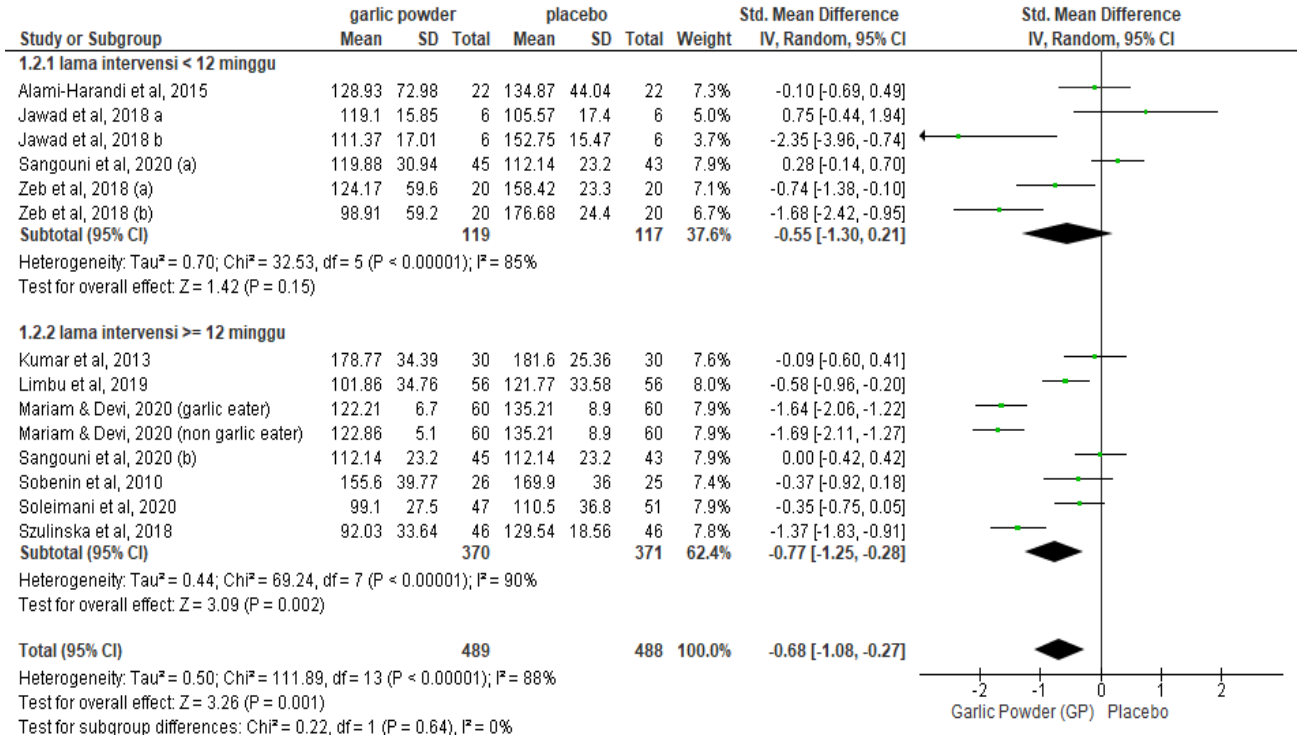

Figure 4 Forest plot meta-analysis of the effect of GP supplementation on LDL levels in patients with hypercholesterolemia

b. Funnel plot

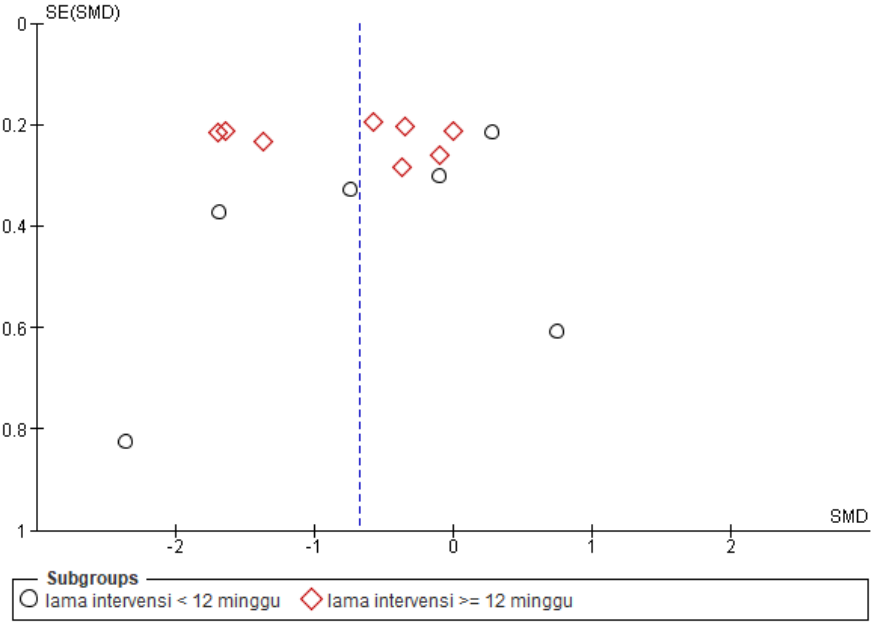

Figure 5 Funnel plot meta-analysis of the effect of GP supplementation on LDL levels in patients with hypercholesterolemia

The funnel plot in Figure 5 shows no publication bias. In the primary study with a small sample size, the distribution of estimates is symmetrical between the right and left of the mean estimation line.

DISCUSSION

The results of the meta-analysis are depicted in a forest plot that contains information about each primary study (sample size, mean, SD, direction of effect), the final estimate of the combined primary study (pooled result) indicated by a diamond image, the direction of the combined effect, intervention significance, Confidence Interval (CI) and heterogeneity between studies (Murti, 2018). In this study, the results of the total analysis showed that GP supplementation significantly reduced TC and LDL levels compared to placebo (diamonds did not touch the midline). The two outcomes had high heterogeneity (I^2 > 50%) which could occur due to differences in race (Europe and Asia), type of GP (enteric coated and ordinary), GP dose (250mg/ day-2000mg/ day), disease/ disease differences. conditions accompanying hypercholesterolemia (obesity, DM, fatty liver, hypertension, coronary heart disease, menopause, pregnancy at risk of pre-eclampsia) and duration of treatment (2 weeks-48 weeks) of each primary study.

The funnel plot is a simple scatter plot that illustrates the relationship between the estimated intervention effects of each primary study (horizontal line) with the study size represented by the standard error/SE (vertical line). The precision of the intervention effect estimation increases as the study size increases and the SE is small. In the funnel plot, studies at the top of the diagram have a larger study size and a smaller SE than studies at the bottom of the diagram. The larger the sample and the smaller the SD, the larger the study size and the more precise the estimation of intervention effects (Murti, 2018; Sterne et al., 2012). Funnel plots are used to determine whether there is publication bias, by looking at the distribution of studies with small sample sizes (the plot is located at the bottom of the diagram). Studies with small sample sizes that are symmetrically distributed between the right and left of the mean estimation line show no publication bias, if the majority is distributed in the direction of the diamond in the forest plot, it will cause overestimation of the intervention effect and if the majority is distributed in the opposite direction to the diamond direction, it will cause an overestimation of the intervention effect. under estimate the effect of the intervention. In a small sample size, the occurrence of events will affect the estimated cumulative effect that has the potential to cause bias compared to a large sample size (Murti, 2018). There was no publication bias in this study.

The difficulty of standardizing active substances is a problem that is still faced by natural medicinal preparations including garlic. There are many factors that are sometimes difficult to control, such as genetic, environmental and processing factors (Prati et al., 2018). Garlic flour is standardized by its allicin content or potential allicin content. Not all primary studies in this study or previous studies include the potential content of allicin in the GP used. In addition, the way of processing GP from fresh garlic is also different so that it affects the potential for allicin content that can be absorbed by the body. Slow-release (enteric-coated) GP tablets are GP dosage forms that are considered to have the best allicin bioavailability because they protect the aliinase enzyme from damage due to gastric acid, so that more allicin is formed from aliin (Bahmani et al., 2015; Ried et al., 2013).

The results of the analysis of total TC are consistent with previous meta-analyses, which showed that GP was more effective in reducing TC compared to placebo (Kwak et al., 2014; Ried et al., 2013). The effectiveness of GP was also seen in the subgroups with an

intervention duration of < 12 weeks and > 12 weeks. This is slightly different from the results of the meta-analysis of Kwak et al (2014), where GP is only effective in reducing TC at the intervention duration >12 weeks. Analysis of total LDL also showed consistency with previous meta-analyses, namely a significant reduction in LDL when compared with placebo. The results of the subgroup analysis are in accordance with the meta-analysis of Kwak et al. (2014), GP is only effective in lowering LDL if given > 12 weeks. According to Kwak et al. (2014), the effectiveness of GP in lowering TC and LDL will be more visible in subjects with hypercholesterolemia/ hyperlipidemia and Asian race compared to subjects with normal fat profile and European race. The subjects in this study were patients with hypercholesterolemia, both primary and secondary, with 8 of the 10 primary studies originating from Asia. In general, GP improves fat profile by inhibiting intra and extra hepatic fat synthesis and increasing lipolysis (Subramanian et al., 2020).

Information regarding the type of food (including garlic) consumed by the subjects during the intervention was found in the primary study by Soleimani et al. (2020), Sangouni et al. (2020), Mariam and Devi (2020), and Alami-Harandi et al. (2015). There were no differences in food intake between the GP and placebo groups in the four primary studies. There were no reported serious side effects of the GP intervention in the 10 primary studies included in this meta-analysis including the group of subjects with 3rd trimester of pregnancy. Garlic flour was well tolerated by the majority of the subjects. The meta-analysis of Kwak et al. (2014) also did not mention any side effects, both mild and severe, caused by GP. As one of the ingredients of food and traditional medicine that has been consumed since centuries ago, garlic's safety has been empirically proven which is strengthened by the findings of this study.

The strength of this study is the focus on the subject of hypercholesterolemia, GP specific intervention, each primary study has a complete outcome fat profile. The limitations of this study are that it only selects English and Indonesian articles, the search for articles is limited to several databases, possible bias due to differences in GP products used which can affect their pharmacodynamics and differences in diseases/-conditions that accompany hypercholesterolemia that can affect the body's response to GP.

The lack of side effects caused by GP as well as its ability to reduce TC and LDL levels in hypercholesterolemic patients as proven in this study can be a consideration for the use of GP in the management of hypercholesterolemia. Further research with better quality, larger sample and population in Indonesia still needs to be done to support the results of this study. The development of standardized GP preparations at affordable prices is still a challenge in the future.

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CONFLICT OF INTEREST

There is no conflict of interest in this research.

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