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# Study of Fermented Food Intervention on the Serum Lipid Profile of Hypercholesterolemia Animals Trial (Meta-analysis)

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***Abstract*— Individuals with hypercholesterolemia (HC) require specific therapy, such as statin medication, to maintain their blood lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C) within the normal range. *In vivo*, studies have shown that consuming fermented foods for a particular duration can help improve the blood lipid profile of HC animal models. However, meta-analysis studies have not investigated which type of fermented food has the most significant effect on improving the blood lipid profile. The studies included were *in vivo* research that examined the effects of fermented food interventions on improving the blood lipid profile in HC animal models. The results of this study indicate that fermented food interventions (both plant-based and animal-based) have a highly significant effect (p-value <0.001) on improving the blood lipid profile compared to the HC animal model group without intervention. However, the plant-based fermented food source group tends to show a more significant effect on lipid profiles than those sourced from animals.**

***Keywords*— Fermented, food, hypercholesterolemia, *in vivo,* lipid**

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## I. INTRODUCTION

Metabolic syndrome (MS) is a disorder of the metabolic system involving the formation and absorption of certain nutrients. Hypercholesterolemia (HC) is one of the non-communicable diseases classified as metabolic syndrome. According to the WHO, an individual categorized as having metabolic syndrome must have at least 3 diagnoses out of its 6 indicators, namely high blood glucose (diabetes), abnormal blood lipids or dyslipidemia (including high cholesterol and triglycerides), hypertension, microalbuminuria, abnormal body mass index, and central obesity [1]. Globally, metabolic syndrome has become a significant health issue and is referred to as a Global Burden of Disease (GBD).

Patients with hypercholesterolemia are concluded with the MS group. The patient has high levels of total blood cholesterol, i.e., >200 mg/dL, with the composition of LDL cholesterol (LDL-C) >190 mg/dL and HDL cholesterol (HDL-C) <35 mg/dL. Similarly, patients with dyslipidemia have excessive levels of one of their blood lipid components, such as cholesterol, cholesterol ester, and phospholipids [2], or triglycerides with levels >150 mg/dL [3,4]. These conditions pose a danger to the human body if not intervened promptly due to HC or dyslipidemia, which can trigger other dangerous complications, such as diabetes, hypertension, stroke, and coronary heart disease [5].

One type of food widely reported to help reduce and control blood cholesterol levels is fermented foods. Several fermented foods such as yogurt, kimchi, kombucha, kefir, and soybean fermentation produce many functional metabolite compounds from their microorganism activities, including organic acids, bioactive peptides, antioxidant components, conjugated linoleic acid, biogenic amines, isoflavones, phytoestrogens, and nattokinase which have hypocholesterolemic effects [6,7].

However, some studies also report that consuming fermented foods cannot significantly improve blood lipid profiles but even have opposite effects. In an *in vivo* study, Kobayashi et al. [8] reported that administering isoflavones derived from fermented soy milk could not inhibit the increase in total cholesterol in hypercholesterolemia test animals, while in the studies by Kameda et al. [9] with tempeh samples, and Yang et al. [10], with frozen yogurt oat samples, in *in vivo* tests also could not improve HDL-C profiles in high-fat diet animals.

Therefore, this study aims to evaluate the effects of various fermented foods interventions on the blood lipid profile of animal models, namely total cholesterol, triglycerides, LDL-C, and HDL-C levels, with hypercholesterolemia/hyperlipidemia conditions through meta-analysis studies. This research will provide information on the most effective fermented foods to improve blood lipid profiles in *in vivo* studies.

## II. METHODS

### *A. Literature Search Strategy*

Journal article searches used 11 international-scale scientific publication search engines with DOIs to facilitate journal retrieval. The 11 search engines used were Science Direct, ACS Publications, PubMed Central, ProQuest, SAGE Journals, MDPI, Semantic Scholar, ResearchGate.net, Hindawi, Wiley, and Taylor & Francis, covering publications from 1995 to 2024 up to January 7, 2024. The search keywords used were: ("Fermented" AND "Cholesterol"), ("*In vivo*" AND "Cholesterol"), ("Fermented Food for Cholesterol"), ("Food" AND "Hypercholesterolemic"), and ("*In vivo*" AND "Hypercholesterol"), searched in the title, abstract, and article keywords.

Journal election was conducted for one month from December 2023 to January 2024, following PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [11], as depicted in Figure 1. The selected articles must meet the following inclusion criteria: (1) *in vivo* studies using animal models (not humans), (2) units that can be converted to mg/dL for all test variables (TC, TG, LDL-C, and HDL-C), (3) precise control and treatment groups, providing information on the number N (repetitions of animal models), and standard deviation information, (4) control animal models must be treated as hypercholesterolemic or hyperlipidemic, (5) feed can be in powder or liquid form and can be given ad libitum or via gavage, and (6) no limitation on the chosen fermented foods, but they should not be a mixture with pure bioactive component supplementation.

### *B. Data Collection*

Data collection from selected articles includes: (1) journal identification (year of publication, DOI, authors, journal name, article title, search engine source), (2) control treatment, type of fermented food intervention, fermentation type, microorganism composition, animal model type, intervention duration, (3) mean values of blood lipid variables, including total cholesterol, triglyceride levels, LDL-C, and HDL-C in control and treatment samples.

The unit used for the four blood lipid variables must be uniform in mg/dL. If the unit in the article is in mmol/L, it must be converted first. Data recording includes the number of samples (N) in control and treatment and recording standard deviation (SD) values. All data are tabulated in Microsoft Excel software.

### *C. Data Analysis*

Meta-analysis data processing was carried out using OpenMEE software [11]. The statistical outcome is in effect size values in Standardised Mean Difference (SMD). The method used in calculating the effect size is the Hedges method with a random-effect model. The effect size values at a 95% confidence interval (CI, Confidence interval) will indicate the magnitude of the differences in the four lipid variables between control samples (without fermented food intervention) and treatment samples (with fermented food intervention). Data heterogeneity was determined through the statistical method of calculating the I2 value [12]. Additionally, publication bias identification was conducted using a funnel plot in the Comprehensive Meta-Analysis (CMA) application.

## III. RESULT AND DISCUSSION

### *D. Literature Search*

After conducting a search using keywords across eleven search engines within the specified publication period (1995 to 2024), a total of 2,685 articles were retrieved for screening based on title and abstract relevance. Subsequently, a thorough assessment was performed on articles matching the criteria in the title and abstract to review their methods and results sections in more detail, identifying 69 selected manuscripts. Further selection was conducted to determine which manuscripts would undergo meta-analysis based on the availability of downloadable articles, consistent unit measurements, appropriate experimental methods, having N (replicates), and standard deviation (SD) values, leading to the identification of 24 selected articles, see **Figure 1**.

During the data extraction phase from the 24 selected articles, with consistent control data and units in line with inclusion criteria, articles were identified based on the type of fermented foods used (pulses, leaves, fruits-vegetables, cereals, cereals+pulses, animal milk, and spices), fermentation type (BAL, mold, acetic acid bacteria), microorganism composition (single and mixed), animal model type (rats, mice, and hamsters), intervention duration (21 - 112 days), intervention feed type (powder and liquid), and country of publication (Indonesia, South Korea, Taiwan, China, Brazil, Japan, Malaysia, India, Saudi Arabia, and Egypt). Subsequently, studies were grouped based on data availability for blood lipid profile variables in each article, revealing 45 studies for total cholesterol variable, 43 for triglycerides, 34 for LDL-C, and 46 for HDL-C.

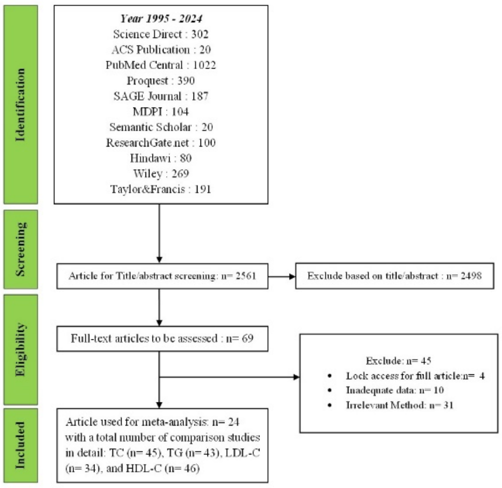

Fig 1. The process of literature search and selection

### E. *The Effect of Fermented Foods on Serum Total Cholesterol (TC)*

The results indicate that fermented foods significantly reduce serum total cholesterol with an SMD value of -4.525 and a 95% CI (-5.473 to -3.577) with a p-value <0.001. A negative SMD value indicates that the intervention group's total cholesterol value at the end of the experiment is lower than the control group's. Therefore, a more significant negative SMD indicates a tremendous difference in total cholesterol between the intervention and control groups. Among the 45 studies from 23 articles used, three studies showed the most significant sequential decreases in total cholesterol: Kobayashi et al. (2014) (II) [8] with soy fermented extract as the intervention feed (23.2% dose in the diet) with an SMD value of -97.107 and a 95% CI (-130.766 to -63.447), followed by Yang et al. (2018) (I) [12] with oat-soy yogurt intervention feed at a 35% dose in the diet with an SMD value of -38.047 and a 95% CI (-49.871 to -26.224), and finally, in the study by Yang et al. (2020) [12] with intervention feed consisting of L. plantarum WW fermented skim milk (10 ml/kg BW dose) with an SMD value of -36.131 and a 95% CI (-48.687 to -23.574), see **Figure 2.**

Total cholesterol is an essential indicator for assessing an individual's risk of heart disease. A total cholesterol value exceeding 200 mg/dL indicates hypercholesterolemia. Martone et al. [13] divided hypercholesterolemic patients into two groups: those with total cholesterol values ranging from 200 to 240 mg/dL are classified as moderately high, and those >240 mg/dL are considered to have very high total cholesterol levels. Higher total cholesterol values increase the risk of death from heart disease and ischemic stroke [14].

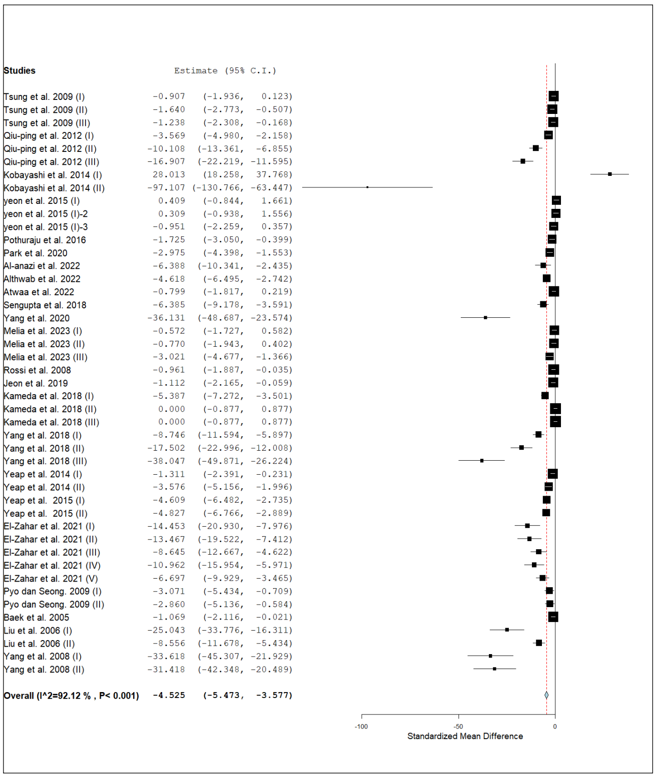

Fig 2. Forest plot effect food fermented on TC

The body naturally maintains cholesterol balance to control normal cholesterol levels. According to Wang et al. [15], there are four mechanisms: (1) controlling cholesterol synthesis within the body, (2) regulating cholesterol absorption from food in the digestive system, (3) converting excess cholesterol into other essential components for the body, such as hormone synthesis, and (4) excreting excess cholesterol. Fermented foods have been reported in many studies to lower high serum cholesterol levels by aiding these cholesterol balance mechanisms. Based on the results of this study, it is known that soy milk extract fermented with BAL has the highest impact on reducing total cholesterol. Intervention in the form of extract provides advantages in higher concentrations of bioactive components because it eliminates contaminating or unwanted components [16].

The fermentation process in soybean milk changes the proximate composition, primarily resulting in reduced fat and carbohydrate levels due to the activity of BAL microorganisms utilizing fat and carbohydrates as energy during fermentation. Thus, fermented soy milk is referred to as an anti-obesity food. Conversely, there is an increase in protein due to hydrolysis during fermentation into amino acids and peptides, as well as an increase in the number of detected BAL microorganisms detected as proteins [17]. Ramdhat et al. [18] and Caponio et al. [19] also reported that soybeans themselves contain many bioactive components from protein fractions such as β-conglycinin (7S globulin) and glycinin (11S globulin) as well as bioactive peptides (FVVNATSN, lunasin, IAVPGEVA, YVVNPDNDEN, IAVPTGVA, and LPYP) that can lower cholesterol levels.

The mechanism of cholesterol reduction by protein compounds may involve disruption of the function of the cholesterol synthesis enzyme HMG-CoA reductase, which acts as an inhibitor or binds to bile acids and cholic acid in the digestive system, excreting them through feces, thereby forcing the body to produce new bile acids using blood cholesterol as raw material [18, 19]. Han et al. [20] also reported that the fermentation process in soy milk significantly increases aglycone isoflavones due to the breakdown of isoflavone glycosides. Aglycone isoflavone has higher antioxidant activity than its glycoside form, and its content can continue to increase with longer fermentation times [21]. Aglycone isoflavones may play a role in reducing blood cholesterol levels. Chadha et al. [22] explained that soy isoflavone compounds can act as anti-atherosclerosis agents by inhibiting oxidative stress, increasing NO availability, reducing LDL size, and preventing the occurrence of oxidized LDL.

### *F. The Effect of Fermented Foods on Triglyceride (TG)*

Triglyceride levels are an essential indicator in blood lipid profiles. In addition to total cholesterol, triglyceride levels correlate with the risk of developing heart disease. Triglyceride components consist of 3 fatty acids and glycerol that comprise most apolipoproteins (VLDL, LDL, chylomicrons, IDL, and HDL) and are hydrophobic [23]. While high-fat foods largely influence total cholesterol, triglycerides differ slightly because, besides fat, carbohydrate components also play a role in increasing triglyceride levels in the blood. Blood triglyceride levels exceeding 150 mg/dL are categorized into 3 groups of hypertriglyceridemia patients: the range of 150 – 199 mg/dL represents patients with moderate TG levels, while levels in the range of 200 – 499 mg/dL indicate patients with high TG levels. If it exceeds 500 mg/dL, it is considered patients with very high TG levels [24].

Meta-analysis results indicate that high triglyceride levels in the blood can be improved by consuming fermented foods. In this study, it was shown that fermented food intervention *in vivo* experiments through meta-analysis with a total of 43 studies yielded significant results in reducing TG with an SMD value of -4.949 and 95% CI (-5.957 to -3.942) and a p-value of <0.001. Three studies out of 43 studies that had the most significant values in decreasing TG levels sequentially were the study by Liu et al. (2006) [25] with an SMD value of -63.439 and 95% CI (-85.441 to -41.437) using an intervention sample of 10% soy milk kefir in the diet, then the study by Yang et al. (2018) [10] with an SMD value of -49.658 and 95% CI (-65.072 to -34.244) using an intervention sample of 35% oat soy yogurt in the diet, and lastly the study by Qiu-ping et al. (2012) [26] with an SMD value of -45.273 and 95% CI (-59.330 to -31.216) using an intervention sample of fermented zijuan tea leaves from China with a dose of 1.1215 g/kg body weight of rats, see **Figure 3.**

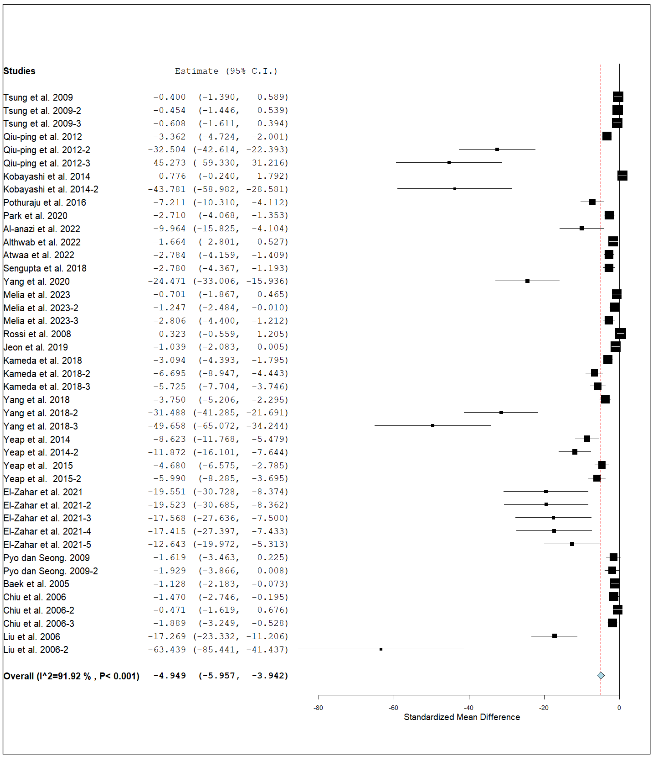

Fig 3. Forest plot effect food fermented on TG

Compared to the fermentation of zijuan tea leaves, polyphenolic compounds are the most dominant bioactive components working in lowering TG. At the same time, soybeans and oats have more diverse bioactive compounds from their fermentation outcomes. However, the numerous bioactive components contained in food ingredients also cannot guarantee a better improvement in lipid profiles. Kameda et al. [9] showed that tempeh, although containing a variety of bioactive components such as fiber, antioxidant components, bioactive peptides, and soy isoflavones, also did not significantly improve serum triglycerides in experimental animals [27]. According to Astawan et al. (2020), the protein quality of soybean tempeh can be enhanced, thereby yielding improved health benefits, through the prior germination of the soybeans [28]

Managing food intake for patients with hypertriglyceridemia is crucial. Reducing calories from fat sources and easily digestible carbohydrates is necessary because excess sugar will enter the pathway of fatty acid synthesis through the breakdown of glucose into Acetyl CoA, which ultimately synthesizes fatty acids that enter the de novo lipogenesis pathway in the liver to form triglycerides [29]. In addition, physical activity can also be done to lower TG levels because the body will use TG in the blood to be transported to the liver and then undergo lipolysis metabolism, where TG is broken down into fatty acids to produce the energy needed during physical activity [30].

### *G. The Effect of Fermented Foods on HDL-C and LDL-C Levels*

High-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) lipid profiles are two essential components that constitute total serum cholesterol in the blood. The ratio between them is more effective in indicating an individual's risk of heart disease than independent measurements of HDL or LDL alone [31]. A study by Hernaez et al. [32] further explains that several factors, including high HDL oxidation, small HDL particle size, high triglyceride content in HDL, and low LDL in resisting oxidation, determine an individual's risk of cardiovascular disease. Therefore, someone with continuously decreasing HDL levels while their LDL levels are increasing will have a higher risk of CVD. According to Retiaty et al. [33], normal HDL levels for men are >40 mg/dL and >50 mg/dL for women, while normal LDL levels are <100 mg/dL.

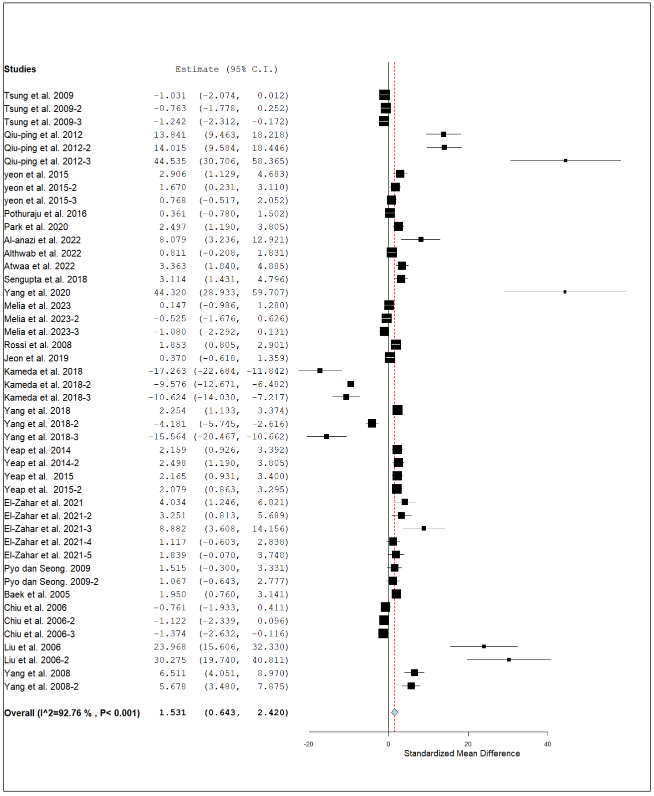

Fig 4. Forest plot effect food fermented on HDL-C

Meta-analysis results show that fermented foods can significantly improve HDL lipid profiles by increasing their levels in 46 studies and reducing LDL levels in 34 studies, with a p-value of <0.001 for each variable. The SMD value for HDL level increase is 1.531 with a 95% CI (0.643 to 2.420), while the SMD value for LDL level decrease is -7.887 with a 95% CI (-9.380 to -6.394). In the forest plot diagram, it can be observed that three studies that had the highest impact on increasing HDL-C values sequentially were: the study by Qiu-ping et al. (2012) [26] with an SMD value of 44.535 and 95% CI (30.706 to 58.365) using fermented Zijuan tea leaf samples at a dose of 1.1215 g/kg BW, then the study by Yang et al. (2020) [12] with an SMD value of 44.320 and 95% CI (28.933 to 59.707) using fermented skim milk samples at a dose of 10 ml/kg BW, and lastly the study by Liu et al. (2006) [25] with an SMD value of 30.275 and 95% CI (19.740 to 40.811) using soy milk kefir samples at a dose of 10% in the diet.

Meanwhile, three studies had the most significant reduction in LDL-C levels; two were the same study by Qiu-ping et al. (2012) [26] using fermented Zijuan tea leaf samples at different doses. The dose of fermented Zijuan tea leaf at 1.1215 g/kg BW showed a better reduction in LDL-C levels compared to the dose of 0.405 g/kg BW, with SMD values and 95% CI sequentially being -65.957 (-86.416 to -45.499) and -59.221 (-77.594 to -40.848). The third study that provided the best reduction in LDL-C was the study by Yang et al. (2018) [10] with an SMD value of -43.608 and 95% CI (-57.151 to -30.066) using oat soy yogurt samples at a dose of 30% in the diet, see **Figure 4** and **5**.

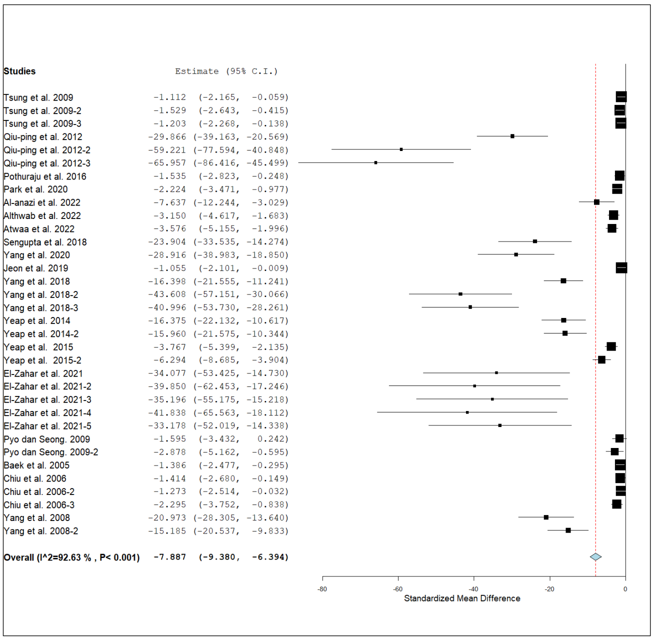

Fig 5. Forest plot effect food fermented on LDL-C

The study reveals that fermented tea leaf samples provide the best intervention in improving both HDL-C and LDL-C lipid profiles. After that, low-fat or skim milk fermentation also has the potential to improve HDL-C profiles, while intervention using fermented oats can only effectively improve LDL-C levels. However, soybean intervention has the potential to improve both by increasing HDL-C levels and reducing LDL-C levels.

The fermentation process of tea leaves involves oxidation, where oxygen molecules from the atmosphere come into contact with enzymes on the leaves, leading to enzymatic reactions between polyphenol oxidase enzymes, peroxidase enzymes, and catechins in the tea, resulting in the formation of oxidized polyphenol compounds namely theaflavins and thearubigins [34]. However, a different condition occurs in the fermentation of Zijuan tea leaves, as reported by Qiu-ping et al. [26], where the fermentation results in a decrease in polyphenol, catechin, theaflavin, and thearubigin content but an increase in large molecule polymer pigment (PPBB) components, which then become something unique and have functional health values in this fermented tea leaf.

Jiang et al. [35] reported that Zijuan tea leaf pigments are rich in anthocyanin compounds, which have antioxidant properties, and one of the anthocyanin pigments, cyanidin-3-O-β-D-glucoside, can increase serum lipid oxidation resistance against lipid peroxidase. Studies reporting that anthocyanin pigments effectively reduce LDL-C levels and increase HDL-C levels have been widely reported [36, 37, 38]. One of the mechanisms is that anthocyanins inhibit the action of the cholesterol synthesis enzyme HMG CoA reductase so that VLDL is not hydrolyzed and LDL can be reduced, while the increase in HDL-C is due to anthocyanins inhibiting CETP (Cholesteryl ester transfer protein), which leads to an increase in HDL-C levels [39]. If CETP is inhibited, there will be no exchange of protein and triglycerides between HDL and VLDL or IDL in the liver, resulting in no new LDL formation.

Improvement of HDL-C Cholesterol Component in the study by Yang et al. [12], with the intervention of fermented skim milk with BAL bacteria, is primarily influenced by the role of probiotic bacteria. Probiotics in the digestive system produce short-chain fatty acids (SCFAs) that can increase the concentration of Apolipoprotein A-I (ApoA-I), which constitutes 70% of the HDL molecule, and enhance the reverse transport process of cholesterol to the liver [40, 41]. On the other hand, oats and soybeans contain bioactive components such as protein, bioactive peptides, fiber, isoflavones in soybeans, and β-glucans in oats that may have a more significant impact on improving HDL-C and LDL-C lipid profiles. According to Joyce et al. [41], β-glucan acts as fiber that inhibits bile acid absorption in the digestive system, thereby increasing bile acid excretion through feces, which results in the body needing to synthesize new bile acids through de novo mechanisms, utilizing blood cholesterol and consequently reducing LDL-C levels.

The mechanism of improving lipid profiles from fermented foods is a contribution from several substances that are only produced from the fermentation process. On the other hand, fermented plant-based ingredients have more pathways for improving blood lipid profiles due to the fermentation process in legumes, cereals, fruits, vegetables, and tea leaves not only contains probiotic bacteria but also results in the formation of many new bioactive components from the fermentation process such as bioactive peptides [42], increased antioxidant compounds [43], or secondary metabolites with hypocholesterolemic effects, as seen in the fermentation of tempeh, which was recently identified through metabolomic studies to contain meglutol compounds (3-hydroxy-3-methylglutarate) that can inhibit cholesterol synthesis enzyme activity [44], see **Figure 6.**

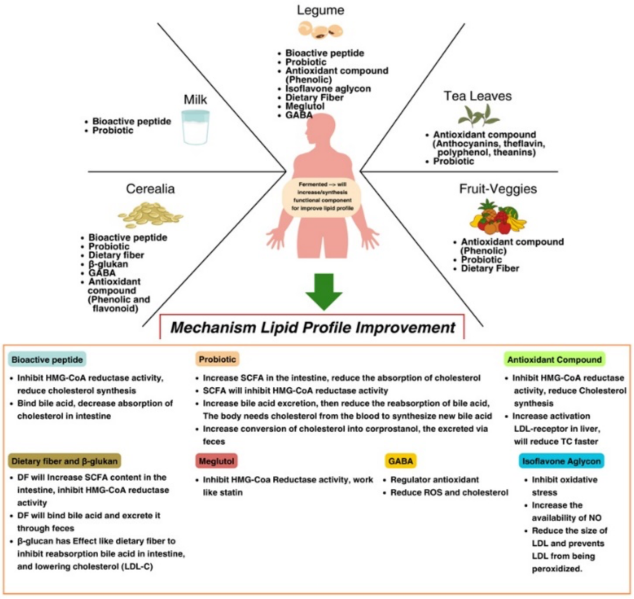

Fig 6. Fermented food improves lipid profile

### *H. Publication Bias*

The meta-analysis bias was measured through funnel plots and Egger's Test values (CMA Software). The analysis of funnel plots showed asymmetric graphs, and Egger's Test yielded p-values < 0.05 for all variables (TC, TG, LDL-C, and HDL-C). This result indicates that the effect size values in the meta-analysis overestimate the actual values and contain bias, thus becoming a limitation of this study. This bias occurs partly due to missing data, where no or limited publications report non-significant data.

## IV. CONCLUSION

The results of the meta-analysis study indicate that *in vivo* interventions with fermented foods in hypercholesterolemic or dyslipidemic animal models can significantly improve blood lipid quality. Both animal-based and plant-based food sources have different effectiveness in lowering total cholesterol, LDL-C, triglycerides, or increasing HDL-C levels. Factors that can influence the success of fermented food interventions in improving blood lipid profiles may include the type of food, duration of intervention, and intervention dosage. Therefore, the findings of this meta-analysis can serve as a reference for developing fermented functional foods for the needs of hypercholesterolemic or hyperlipidemic patients.

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## CONFLICT OF INTEREST

Authors declare no conflict of interest to disclose. The authors confirm that no generative AI or AI-assisted tools were used in the preparation of this manuscript.

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TABLE 1.

STUDIES INCLUDED AS A DATABASE FOR META-ANALYSIS OF INTERVENTION FERMENTATION FOOD FOR HYPERCHOLESTEROLEMIC/HYPERLIPIDEMIC ANIMAL

| **No** | **Authors** | **Food Intervention** | **Source ofFood** | **Type of Sample** | **Type of Microorganism** | **Composition of Microorganism** | **Name of Microorganism** | **Duration of Treatment** | **CountryOrigin** |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Baek *et al*. 2005 [45] | Brown Rice | Plant (Cereal) | Powder | LAB | Single | *L. acidophilusKCTC 2182* | 28 Days | Korea |
| 2 | Chiu *et al*. 2006 (1) [46] | Cow Skim Milk | Animal (Milk) | Liquid | LAB | Single | *L. paracasei subsp. paracasei NTU 101* | 56 Days | Taiwan |
| 3 | Chiu *et al*. 2006 (2) [46] | Cow Skim Milk | Animal (Milk) | Liquid | LAB | Single | *L. plantarum NTU 102* | 56 Days | Taiwan |
| 4 | Chiu *et al*. 2006 (3)[46] | Cow Skim Milk | Animal (Milk) | Liquid | LAB | Single | *L. acidophilus BCRC 17010.* | 56 Days | Taiwan |
| 5 | Liu *et al*. 2006 (1) [25] | Cow Kefir | Animal (Milk) | Powder | Kefir Grain | Mixture | *Bakteri dan Yeast* | 56 Days | Taiwan |
| 6 | Liu *et al*. 2006 (2) [25] | Soy Kefir | Plant (Pulse) | Powder | Kefir Grain | Mixture | *Bakteri dan Yeast* | 56 Days | Taiwan |
| 7 | Rossi *et al*. 2008 [47] | Soymilk | Plant (Pulse) | Liquid | LAB | Mixture | *Enterococcus faecium dan L. helveticus ssp jugurti 416* | 60 Days | Brazil |
| 8 | Yang *et al*. 2008 (1) [48] | Black Tea | Plant (Leaves) | Liquid | AAB | Single | *Gluconacetobacter sp* | 84 Days | China |
| 9 | Yang *et al*. 2008 (2) [48] | Black Tea | Plant (Leaves) | Liquid | MOLD/FUNGI | Single | *Mold/Fungi (Fungus Tea)* | 84 Days | China |
| 10 | Tsung *et al*. 2009 [49] | Soymilk | Plant (Pulse) | Liquid | LAB | Mixture | *Lactobacillus paracasei subsp. paracasei NTU 101 and Lactobacillus plantarum NTU 102* | 56 Days | China |
| 11 | Pyo dan Seong.2009 [50] | Soybean | Plant (Pulse) | Liquid | MOLD/FUNGI | Single | *Monascus Sp* | 40 Days | Korea |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 12 | Qiu-ping *et al.* 2012 [26] | Zijuan LeavesTea | Plant (Leaves) | Liquid | Natural Microbes | - | - | 45 Days | China |
| 13 | Kobayashi et al. 2014 [8] | Soymilk | Plant (Pulse) | Powder | LAB | Single | *Lactobacillus delbrueckii subsp. delbrueckii strain of TUA-4408L (SNC33)* | 35 Days | Japan |
| 14 | Yeap et al. 2014 [51] | Angkak | Plant (Cereal) | Powder | MOLD/FUNGI | Single | *Monascus purpureus* | 70 Days | Malaysia |
| 15 | Yeon et al. 2015 [52] | Pepper | Plant (Spices) | Powder | LAB | Single | *Bacillus licheniformis SK1230* | 63 Days | Korea |
| 16 | Yeap et al. 2015 [53] | Mungbean | Plant (Pulse) | Powder | MOLD/FUNGI | Single | *Rhizopus Sp* | 70 Days | Malaysia |
| 17 | Pothuraju et al. 2016 [54] | Cow Skim Milk | Animal (Milk) | Liquid | LAB | Single | *Lactobacillus plantarum NCDC 625* | 84 Days | India |
| 18 | Sengupta et al. 2018 [55] | Soymilk | Plant (Pulse) | Powder | LAB | Mixture | *(Lactobacillus delbrueckii subsp. bulgaricus and Streptococcus thermophilus* | 56 Days | India |
| 19 | Kameda et al. 2018 (1) [9] | Tempe | Plant (Pulse) | Powder | MOLD/FUNGI | Single | *Rhizopus Species Oligosporus* | 21 Days | Japan |
| 20 | Kameda et al. 2018 (2) [9] | Tempe | Plant (Pulse) | Powder | MOLD/FUNGI | Single | *Rhizopus Species oryzae* | 21 Days | Japan |
| 21 | Kameda et al. 2018 (3) [9] | Tempe | Plant (Pulse) | Powder | MOLD/FUNGI | Single | *Rhizopus Species stolonifer* | 21 Days | Japan |
| 22 | Yang et al. 2018 [10] | Oat Soy | Plant (Mixture Cereal + Pulse) | Powder | LAB | Mixture | *Bifidobacterium and Lactobacillus acidophilus* | 112 Days | China |
| 23 | Jeon et al. 2019 [56] | Cabbage and Appel | Plant (Fruit and Vegetable) | Liquid | LAB | Single | *L. plantarum EM* | 42 Days | Korea |
| 24 | Park et al. 2020 [57] | Cabbage and Appel | Plant (Fruit and Vegetable) | Liquid | LAB | Single | *L. Plantarum* | 56 Days | Korea |
| 25 | Yang et al. 2020 [12] | Cow Skim Milk | Animal (Milk) | Liquid | LAB | Single | *L. plantarum WW* | 84 Days | China |
| 26 | El-Zahar et al. 2021 [58] | Camel milk | Animal (Milk) | Liquid | LAB | Single | *Bifidobacterium longum BB536 (Single)* | 28 Days | Saudi Arabia - Mesir |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 27 | El-Zahar et al. 2021 (1) [59] | Camel milk | Animal (Milk) | Liquid | LAB | Mixture | *S. thermophulis, L. bulgaricus (Mixture)* | 28 Days | Saudi Arabia - Mesir |
| 28 | El-Zahar et al. 2021 (2) [59] | Camel milk + cow milk | Animal (Milk) | Liquid | LAB | Mixture | *S. thermophulis, L. bulgaricus (Mixture)* | 28 Days | Saudi Arabia - Mesir |
| 29 | El-Zahar et al. 2021 (3) [59] | Camel milk + cow milk | Animal (Milk) | Liquid | LAB | Single | *Bifidobacterium longum BB536 (Single)* | 28 Days | Saudi Arabia - Mesir |
| 30 | Al-anazi et al. 2022 [60] | Camel milk | Animal (Milk) | Liquid | LAB | Mixture | *S. thermophilus and L. bulgaricus* | 42 Days | Saudi Arabia - Mesir |
| 31 | Althwab et al. 2022 [61] | Camel skim milk | Animal (Milk) | Powder | LAB | Mixture | *Lactobacillus bulgaricus and Streptococcus thermophilus* | 56 Days | Saudi Arabia - Mesir |
| 32 | Atwaa et al. 2022 [62] | Camel skim milk | Animal (Milk) | Liquid | LAB | Mixture | *Streptococcus thermophiles, Lactobacillus acidophilus, and Bifidobacterium bifidum* | 56 Days | Mesir |
| 33 | Melia et al. 2023 [63] | Goat milk | Animal (Milk) | Liquid | LAB | Single | *Pediococcus acidilactici* | 21 Days | Indonesia |

TABLE 2.

EXPERIMENTAL INFORMATION REPORTED IN DATABASE STUDIES

| **No** | **Authors** | **N Sample** | **Total Cholesterol** | **Triglyceride** | **LDL-C** | **HDL-C** |
|---|---|---|---|---|---|---|
| 1 | Baek *et al.* 2005 | 8 | √ | √ | √ | √ |
| 2 | Chiu *et al.* 2006 (1) | 6 | - | √ | √ | √ |
| 3 | Chiu *et al.* 2006 (2) | 6 | - | √ | √ | √ |
| 4 | Chiu *et al.* 2006 (3) | 6 | - | √ | √ | √ |
| 5 | Liu *et al.* 2006 (1) | 8 | √ | √ | - | √ |
| 6 | Liu *et al.* 2006 (2) | 8 | √ | √ | - | √ |
| 7 | Rossi *et al.* 2008 | 10 | √ | √ | - | √ |
| 8 | Yang *et al.* 2008 (1) | 8 | √ | - | √ | √ |
| 9 | Yang *et al.* 2008 (2) | 8 | √ | - | √ | √ |
| 10 | Tsung *et al.* 2009 | 8 | √ | √ | √ | √ |
| 11 | Pyo dan Seong. 2009 | 3 | √ | √ | √ | √ |
| 12 | Qiu-ping *et al.* 2012 | 10 | √ | √ | √ | √ |
| 13 | Kobayashi *et al.* 2014 | 8 | √ | √ | - | - |
| 14 | Yeap *et al.* 2014 | 8 | √ | √ | √ | √ |
| 15 | yeon *et al.* 2015 | 5 | √ | - | - | √ |
| 16 | Yeap *et al.* 2015 | 8 | √ | √ | √ | √ |
| 17 | Pothuraju *et al.* 2016 | 6 | √ | √ | √ | √ |
| 18 | Sengupta *et al.* 2018 | 6 | √ | √ | √ | √ |
| 19 | Kameda *et al.* 2018(1) | 10 | √ | √ | - | √ |
| 20 | Kameda *et al.* 2018 (2) | 10 | √ | √ | - | √ |
| 21 | Kameda *et al.* 2018 (3) | 10 | √ | √ | - | √ |
| 22 | Yang *et al.* 2018 | 10 | √ | √ | √ | √ |
| 23 | Jeon *et al.* 2019 | 8 | √ | √ | √ | √ |
| 24 | Park *et al.* 2020 | 8 | √ | √ | √ | √ |
| 25 | Yang *et al.* 2020 | 8 | √ | √ | √ | √ |
| 26 | El-Zahar *et al.* 2021(1) | 3 | √ | √ | √ | √ |
| 27 | El-Zahar *et al.* 2021 (2) | 3 | √ | √ | √ | √ |
| 28 | El-Zahar *et al.* 2021 (3) | 3 | √ | √ | √ | √ |
| 29 | El-Zahar *et al.* 2021 (4) | 3 | √ | √ | √ | √ |
| 30 | Al-anazi *et al.* 2022 | 3 | √ | √ | √ | √ |
| 31 | Althwab *et al.* 2022 | 8 | √ | √ | √ | √ |
| 32 | Atwaa *et al.* 2022 | 8 | √ | √ | √ | √ |
| 33 | Melia *et al.* 2023 | 6 | √ | √ | - | √ |

TABLE 3.

DOSAGE AND CONTROL TREATMENT OF IN VIVO STUDY FOR META ANALYSIS

| No Paper | Authors | Food Sample (Cholesterol Diet Intervention) | Dosage | Control Sampel |
|---|---|---|---|---|
| 1 | Baek *et al.* 2005 | Brown rice fermented | 50/100 g Animal Feed | High cholesterol diet (1% cholesterol) |
| 2 | Liu *et al.* 2006 (1) | Milk kefir | 10% in diet | High cholesterol diet (0,35% cholesterol) |
|  | Liu *et al.* 2006 (2) | Soyamilk kefir | 10% in diet |  |
| 3 | Chiu *et al.* 2006 (1) | Milk fermented *L paracasei* | NA | High Cholesterol Diet (5% Cholesterol and 0,3% bile salt) |
|  | Chiu *et al.* 2006 (2) | Milk fermented *L plantarum* | NA |  |
|  | Chiu *et al.* 2006 (3) | Milk fermented *L acidophilus* | NA |  |
| 4 | Yang *et al.* 2008 (1) | Kombucha *Gluconacetobacter sp* | NA | High Cholesterol Diet (10 g/Kg Cholesterol, lard oil 100 g/Kg, Cholate 1 g/Kg) |
|  | Yang *et al.* 2008 (2) | Kombucha tea fungus | NA |  |
| 5 | Rossi *et al.* 2008 | Soy fermented | 1mL/day | High Cholesterol Diet (Cholesterol 1% dan 0.25% cholic acid ) |
| 6 | Pyo dan Seong. 2009 (1) | Soybean fermented extract | 200mg/kg bw | High Cholesterol and High Fat Diet [pig oil (10% w/w), powdered egg yolk (10% w/w), cholesterol (1% w/w), and bile salt (0.2% w/w)] |
|  | Pyo dan Seong. 2009 (2) | Soybean fermented extract | 400 mg/kg bw |  |
| 7 | Tsung *et al.* 2009 (1) | Soymilk fermentation *L plantarum NTU 101* | 4,5 g/kg | High cholesterol diet (cholesterol 0,2%) |
|  | Tsung *et al.* 2009 (2) | Soymilk fermentation *L plantarum NTU 102* | 4,5 g/kg |  |
|  | Tsung *et al.* 2009 (3) | Soymilk | 4,5 g/kg |  |
| 8 | Qiu-ping *et al.* 2012 (1) | Fermented zijuan tea | 0.135 g/kg BW | High Fat Diet (lard oil 10%, yolk powder 10%, cholesterol 0,1%, bile salt 0,2%) |
|  | Qiu-ping *et al.* 2012 (2) | Fermented zijuan tea | 0.405 g/kg BW |  |
|  | Qiu-ping *et al.* 2012 (3) | Fermented zijuan tea | 1.1215 g/kg BW |  |
| 9 | Kobayashi *et al.* 2014 (1) | Soy fermented extract | 4% in diet | High cholesterol diet (cholesterol 1%) |
|  | Kobayashi *et al.* 2014 (2) | Soy fermented | 23.2% in diet |  |
| 10 | Yeap *et al.* 2014 (1) | Red yeast extract fermented | 6 mg/kg bw | High Cholesterol Diet (1000 mg/Kg) |
|  | Yeap *et al.* 2014 (2) | Red yeast extract fermented | 60 mg/kg BW |  |
| 11 | Yeap *et al.* 2015 (1) | Mung bean fermented | 200mg/kg BW | High Cholesterol Diet ( 1g/Kg BW) |
|  | Yeap *et al.* 2015 (2) | Mung bean fermented | 1000 mg/kg BW |  |
| 12 | yeon *et al.* 2015 (1) | Yoghurt | 2% in diet | High Cholesterol and High Fat Diet (Lard 20,38%, Cholesterol 0,98%, cholin acid 0,49%) |
|  | yeon *et al.* 2015 (2) | Pepper juice fermented | 2% in diet |  |
|  | yeon *et al.* 2015 (3) | Pepper juice fermented | 5% in diet |  |
| 13 | Pothuraju *et al.* 2016 | Skim milk feremneted *L plantarum Lp 625* | NA | High fat diet (lard 28%) |
| 14 | Sengupta *et al.* 2018 | Soy yoghurt | 8,5% in diet | High Cholesterol and High Fat Diet (Animal Fat 31.70 g, Cholesterol 1,25%,, cholic acid 0,5%) |
| 15 | Kameda *et al.* 2018 (1) | Tempe R*hizopus oligosporus* | 20% in diet w/w | High fat diet |
|  | Kameda *et al.* 2018 (2) | Tempe *R. oryzae* | 20% in diet w/w |  |
|  | Kameda *et al.* 2018 (3) | Tempe *R stolonifer* | 20% in diet w/w |  |

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| 16 | Yang *et al.* 2018 (1) | Oat soy yoghurt | 25% in diet | High Fat Diet (10% lard oil, 2% yolk powder, 2% cholesterol) |
| | Yang *et al.* 2018 (2) | Oat soy yoghurt | 30% in diet | |
| | Yang *et al.* 2018 (3) | Oat soy yoghurt | 35% in diet | |
| 17 | Jeon *et al.* 2019 | Cabbage appler juice fermentation | 1 mL/day | High Cholesterol and High Fat Diet (Animal Fat 17%, Cholesterol 1%) |
| 18 | Park *et al.* 2020 | Cabbage apple fermentation | 10 ml/Kg BW | High fat diet |
| 19 | Yang *et al.* 2020 | Skim milk feremneted *L plantarum WW* | 10mL/Kg BW | High Fat Diet (10% lard, 2% cholesterol, and 0.3% sodium cholate) |
| 20 | El-Zahar *et al.* 2021 (1) | Camel + cow milk fermented *Bifidiobacterium* | 2mL/day | High Fat Diet (31.75 g animal fat, 1% cholesterol, and 0.25% bile acids (w/w) to every 67.5 g of basal diet) |
| | El-Zahar *et al.* 2021 (2) | Camel milk fermented *Bifidiobacterium* | 2mL/day | |
| | El-Zahar *et al.* 2021 (3) | Camel + cow milk fermented tradisional culture | 2mL/day | |
| | El-Zahar *et al.* 2021 (4) | Camel milk + tradisional culture | 2mL/day | |
| | El-Zahar *et al.* 2021 (5) | Cow milk fermented + tradisional culture | 2mL/day | |
| 21 | Al-anazi *et al.* 2022 | Camel milk fermented | 2 mL/day | High Cholesterol and High Fat Diet (Animal Fat 31.70 g, Cholesterol 1%, bile acid 0,3%) |
| 22 | Althwab *et al.* 2022 | Camel milk fermented | 4% in diet | High cholesterol diet (1% cholesterol) |
| 23 | Atwaa *et al.* 2022 | Camel milk fermented | 10g/day | High Cholesterol and High Fat Diet (Animal Fat 31.70 g, Cholesterol 1%, bile acid 0,3%) |
| 24 | Melia *et al.* 2023 (1) | Cowmilk fermented | 0.35 mL/day | High fat diet (egg yolk) |
| | Melia *et al.* 2023 (2) | Cowmilk fermented | 0.70 mL/day | |
| | Melia *et al.* 2023 (3) | Cowmilk fermented | 1.05 mL/day | |