Effectiveness of chitosan as a dietary supplement in lowering cholesterol in murine models: A meta-analysis

Sung-Il Ahn, Sangbuem Cho, and Nag-Jin Choi*

Department of Animal Science, Jeonbuk National University, Jeonju 54896, Korea

Corresponding author: Nag-Jin Choi, Department of Animal Science, Jeonbuk National University, Jeonju 54896, Korea

Tel: +82-63-270-2579; Fax: +82-63-270-2612

E-mail: nagjin@jbnu.ac.kr

Abstract

This study presents a meta-analysis of studies that investigate the effectiveness of chitosan administration on lifestyle-related disease in murine models. A total of 34 published studies were used to evaluate the effect of chitosan supplementation. The effect sizes for various items after chitosan administration were evaluated using the standardized mean difference. Using Cochran's Q test, the heterogeneity of effect sizes was assessed, after which a meta-ANOVA and –regression test was conducted to explain the heterogeneity of effect sizes using the mixed-effect model. Publication bias was performed using Egger's linear regression test. Among the items evaluated, blood triglyceride and HDL-cholesterol showed the highest Q statistics and I^2 values, respectively. Other than blood HDL-cholesterol, total cholesterol, and triglyceride in feces, most items evaluated showed a negative effect size with high significance in the fixed- and random-effect model ($p<0.0001$). In the meta-ANOVA and -regression test, administering chitosan and resistant starch was revealed to be most effective in lowering body weight. In

addition, chitosan supplementation proved to be an effective solution for TNF-α inhibition. In conclusion, chitosan has been shown to be somewhat useful in improving symptoms of lifestyle-related disease. Although there are some limitations in the results of this meta-analysis due to the limited number of animal experiments conducted, chitosan administration nevertheless shows promise in enhancing the quality of human life.

Keywords: meta-analysis, chitosan, lifestyle-related disease, cholesterol lowering

1. Introduction

Lifestyle-related diseases, including obesity, hyperlipidemia, atherosclerosis, type II diabetes, and hypertension, are widespread in industrialized countries, and are major threats to cardiovascular health. The syndrome is related to a combination of metabolic disorders, including abdominal obesity, hypertriglyceridemia, high-density lipoprotein (HDL) cholesterol decrease, hypertension, and high blood glucose, which lead to increased cardiovascular morbidity and mortality (Grundy et al., 2005). Unnatural blood lipid levels such as high levels of total cholesterol (TC) or triglyceride (TG), high low-density lipoprotein (LDL) level, or low HDL-cholesterol level are correlated with heart disease and stroke. Hypertension is one of the harmful risk factors for stroke and is a key factor in heart attacks. Moreover, obesity acts as a significant risk factor for cardiovascular disease and susceptibility to diabetes (Thayer et al., 2010). Thus, there is an urgent need for food additives that are effective in controlling these health-related parameters.

Chitosan is one of the polymers containing acetyl glucosamine and glucosamine. It may be obtained by hydrolyzing and converting with alkali from crabs, shrimps, insects, mushrooms, and the cell walls of microorganisms. Chitosan manufacture by deacetylation of chitin has been

utilized in wastewater treatment or the agricultural sector. As the safety of chitin or chitosan become increasingly recognized, it has recently been used in a variety of fields, including medical supplies, food additives, and cosmetics (Austin et al., 1980; Jeon and Kim, 2001). Chitosan is also known among food additives whose effects include lowering blood or liver cholesterol and triglyceride by combining with lipids (Koide, 1998). It even shows an anti-inflammatory effect by TNF-α inhibition (Kim et al., 2004; Seo et al., 2003; Yermak et al., 2005; Knorr, 1991).

Studies of lifestyle diseases in murine models suggest that they may be improved by administering chitosan. However, few comprehensive studies have been conducted to date on the effect of chitosan supplementation on improving lifestyle diseases. Accordingly, the objective of the present study was to perform a meta-analysis of the effects of chitosan on factors in lifestyle-related diseases in adults.

2. Results

2.1. Data set

Table 1 shows the data sets and experimental conditions for the 34 published studies used in the meta-analysis. The publication years of the studies ranged between 1978 and 2020. The animals most frequently used in the data set were rat strains such as Sprague-Dawley and Wistar, experiment duration was distributed between 2.8 and 21 weeks, and experimental diet most used for inducing hyperlipidemia in the data set was a high fat/cholesterol diet. In the case of Liu et al. (2015), a high-fructose diet was used to induce hyperlipidemia. Other than the study of Gallaher et al. (2000), blood total cholesterol (TC) was observed in all studies. In addition

to total triglyceride (TG), low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol in the blood, TC and TG in the liver, and fecal TC and TG were investigated. The levels of chitosan administered to hyperlipidemia-induced animals ranged from 0.045 to 7.5%. The chitosan administration period varied between 3 and 21 weeks.

2.2. Effect size and heterogeneity

The effect sizes of chitosan administration on hyperlipidemia in murine models using fixed and random effect models are listed in Table 2. Most items other than HDL-cholesterol in blood, total cholesterol, and triglyceride in feces showed negative effect size and high significance ($p < 0.0001$) in both effect models. These results mean that chitosan administration results in decreased levels of TC, TG, and LDL-C in blood, TC and TG in the liver, TNF-α and glucose in blood and body weight, and increased levels of blood HDL-C, fecal TC and TG.

2.3. Moderator analysis

Since heterogeneity analysis in this study revealed a high level of heterogeneity between the studies analyzed, moderator analysis was performed to account for this. For this, meta-ANOVA and meta-regression were conducted. To perform the meta-ANOVA test, Q statistics between the subgroups (Q_b) calculated under assessing that between subgroups (τ^2) was the same. First of all, a meta-ANOVA analysis was performed on most items except fecal TG, as shown in Table 3 and 4. CTS+RS showed the highest effect size in blood TC and TG, body weight, blood glucose and blood HDL-C, CTS showed the largest effect size in blood LDL-C and TNF-α, and the CSR and WSC showed the greatest effect size in liver TC and liver TG, respectively (Table 3). However, none of these items was statistically significant ($p<0.05$). Table 4 shows the results of meta-ANOVA in analyzing the effect of chitosan administration period on biological indices ($p<0.05$). Other than fecal TC, body weight, and blood glucose,

most items showed significant differences ($p<0.05$). In the case of TC, the Q statistics between the groups (Q_b) was 31.94 (df = 13, $p=0.0025$); the effect size between groups was assumed to be significantly different.

Next, meta-regression was performed to evaluate the effect size between the type of chitosan used and the administration period (Table 5). Only CTS+RS was significant ($p=0.0208$), and it was revealed to use to decrease blood TC. In the case of WSC, it was significantly effective in TNF-α and body weight ($p=0.0307$ and 0.0008, respectively). With regard to the administration period, this was significantly relevant to blood HDL-C and liver TC with $p=0.0004$ and 0.0358, respectively. However, their R^2 values were below 22.33%, which means that the regression models were of low explanatory power.

2.4. Publication bias

Publication bias was conducted using a funnel plot (Figure 1) and an Egger's linear regression test (Table 6) on blood TC and TG, blood LDL-C and HDL-C, liver TG and TC, fecal TC, and body weight. As shown in. Figure 1, publication bias was observed in all items. As the results from the Egger's linear regression test show, significance was detected in all items ($p<0.05$) indicating that the relationship between effect size and standard error was statistically significant and confirming the presence of publication bias (Egger et al., 1997). Thus, the trim-and-fill technique was used to correct asymmetry due to publication bias in all items, with the resulting compensated effect sizes being shown in Table 7. Other than blood HDL-C, most of the effects showed significance ($p<0.05$).

3. Discussion

In the results of Table 2, most items showed negative effect size and high significance ($p <$ 0.0001) in both effect models. These results mean that chitosan administration results in decreased levels of TC, TG, and LDL-C in blood, TC and TG in the liver, TNF-α and glucose in blood and body weight, and increased levels of blood HDL-C, fecal TC and TG.

The bioavailability of dietary fat in the intestine decreased after chitosan administration. After this, reverse cholesterol transport, which is delivered from peripheral tissues to the liver, is accelerated by catabolism and excretion of surplus dietary fat, resulting in an increase in the ratio of HDL-cholesterol (Razdan and Petterson, 1994). In similar vein, Lee et al. (1998) have reported that the addition of chitosan to an animal diet caused a decrease in LDL-cholesterol content. Generally, HDL-cholesterol may decrease cardiovascular disease by converting cholesterol condensed on peripheral tissues or blood vessel walls into an ester compound. The ester compound is then transferred to the liver, excreted by bile-salt, and cholesterol content in blood is lowered. By contrast, LDL-cholesterol, which is the most general delivery type of blood cholesterol, accumulates quickly on artery walls, causing arteriosclerosis. For this reason, it is known as the leading risk factor for arteriosclerosis and cardiovascular disease (Gordon et al., 1981). In this result, increased HDL-cholesterol, fecal total cholesterol, and triglyceride after chitosan administration are related to the factors mentioned above. According to Jeon and Kim (2001), when chitosan is cationized ($-NH3^+$), its viscosity is increased by the formation of polyanions and gels. In high viscosity of the intestine, dietary fiber lower blood cholesterol by delaying cholesterol diffusion from micelle to mucosa, inhibiting bile acid metabolism, delaying micelle forming, and reducing cholesterol absorption rate in the intestine (Vahouny et al., 1983; Furda, 1990; Johnson and Gee, 1981). Based on this result, chitosan exhibits an

excellent anti-hypercholesterolemic effect and is thought to be effective in mitigating cardiovascular disease caused by excessive fat intake.

Nauss et al. (1983) assume that chitosan binds lipid micelle in the small intestine after the ingestion of a fatty meal, while Kanauchi et al. (1995) propose a more specific mechanism by which chitosan inhibits fat digestion in the gastrointestinal tract. In the stomach, chitosan is dissolved in acidic gastric juice. In this aqueous phase, it acts as an emulsifier on fat globules, and may have strong emulsifying properties. It also mixes with fat to form an emulsion. Once transferred into the intestine, the chitosan in the emulsion turns into an insoluble gel-like form trapped in fat, which cannot be decomposed by enzymes such as pancreatin or other intestinal enzymes. As a result, fat excretion in feces is increased (Figure 2). In this connection, Gallaher et al. (2000) have confirmed that in one animal study chitosan administration led to fecal fat excretion approximately 7.5 times higher compared to that of a cellulose-fed group.

Cytokines are secreted by activated lymphocytes and macrophages, and regulate the function of the cells related to immune response. They are also recognized as playing an essential role in the inflammatory response (Zhang and An, 2007). Yemak et al. (2005) report that TNF-α generation was lower in lipopolysaccharide (LPS) and chitosan-injected mice than in LPS-injected mice. Similarly, Seo et al. (2003) observe that TNF-α was increased by the application of special stimulants in a human mast cell line (HMC-1), but decreased by the use of chitosan. TNF-α is one of the pro-inflammatory cytokines synthesized by adipose tissue (Freid et al., 1998; Mohammed-Ali et al., 1997), and high TNF-α levels are one of the critical risk factors for diabetes (Ziamajidi et al., 2017). In similar vein, Yoon et al. (2007) state that chitosan is associated with an anti-inflammatory response to TNF-α gene expression. According to Zhu et al., (2015), chitosan has an anti-inflammatory effect on active molecules,

for example TNF-α and IL-1β via the NF-κB pathway. Activated macrophages secrete numerous pro-inflammatory cytokines, including IL-1β and TNF-α, to intermediate the inflammatory response (Lin and Karin, 2007). However, overproduction of these pro-inflammatory mediators causes excessive inflammation (Lawrence et al., 2002); thus, regulation of the release of pro-inflammatory mediators may be important in mitigating the inflammatory response.

According to Prabu and Naturajan (2017), blood glucose levels decreased in streptozotocin-induced diabetic rats that were fed chitosan for 30 days. Other researchers suggest that the effectiveness of chitosan in lowering blood glucosemay be due in part to the effect of total glyceride in lowering free fatty acids. Jo et al. (2013) report that in an *in vitro* animal study, chitosan that was enzymatically treated and of low molecular weight (< 1,000 Da) was more effective in managing prandial glucose. Kim et al. (2014) also report that chitosan that is low in molecular weight acted similarly to acarbose, a known anti-diabetic medication, in a murine model. They also note that chitosan administration inhibited sucrase and glucoamylase activities. It is recognized that chitosan binds with glucosidase in the intestinal brush border in a manner similar to acarbose (Hanefeld, 2007; Puls et al., 2007; Krentz and Bailey, 2004). The inference of these reports is that body weight may be decreased by chitosan administration.

Meta-analysis is a method of statistical analysis that combines results from various scientific studies to obtain a quantified synthesis (Greenland, 2008). Meta-analysis increases the power of statistical analysis by pooling the results from multiple available studies. In the course of this process, heterogeneity is introduced as a result of methodological differences between studies. In general, a heterogeneity test is used to decide on methods for combining

studies and to evaluate the consistency or inconsistency of findings (Petitti, 2001; Higgins et al., 2002). To evaluate heterogeneity in relation to effect size in the present study, Q statistics and I^2 values were computed. The highest among Q statistics was TG in blood, with high significance ($p<0.0001$). The significance of the Q statistic implies that the studies used to calculate overall effect (the effect size of fixed and random effect models) do not share the same effect size with one another (Cho et al., 2012). In this study, the Q statistics for all items were found to be significant ($p<0.0001$). However, one limitation of this method is its dependence on the number of studies (Fleiss, 1986). I^2 and τ^2 values are commonly used to overcome this limitation of Q statistics by providing a concrete indication of heterogeneity. The I^2 value is used most frequently in meta-analysis to compare different numbers of studies and data types. Consequently, it offers a solution to the issue of the Q statistic when analyzing heterogeneity (Higgins et al., 2003). All items of I^2 value in the present study were above 70%, which means that they all showed significant levels of heterogeneity (Ahn et al., 2020). The τ^2 value indicates the absolute value of heterogeneity, representing variance in true effect sizes (Tufanaru et al., 2019). In addition, liver TG showed the highest τ^2 value, which means that variance in the effectiveness of chitosan administration is great (Cho et al., 2012).

Cholestyramine and cholestipol as an anion-exchanger are these days used mainly for reducing cholesterol. These medications contain amino groups, are water-insoluble, and unlike chitosan are not absorbed in the intestine. Consequently, they are known to inhibit cholesterol absorption in the gut and to promote bile salt excretion. However, they are also known to involve a number of issues, including gastrointestinal disturbance, constipation, and colon cancer (Clementi and Weber-Schondorfer, 2015; Jennings et al., 1988). Valhouny et al. (1983) reports that chitosan supplementation showed a similar inhibition effect to cholestyramine in

cholesterol absorption. Similarly, an animal study by Jennings et al. (1988) showed that chitosan was similar to cholestyramine in lowering lipids without other harmful changes in intestinal mucosa. It can thus be concluded that chitosan supplementation may be useful in lowering cholesterol and offers a promising alternative treatment for lifestyle-related diseases.

4. Materials and methods

4.1. Data set

To perform a meta-analysis of published studies regarding the effect of chitosan administration on lowering cholesterol in murine models between 1978 to 2020, a literature search was conducted on Pubmed (US National Library of Medicine, Bethesda, MD) and Science Direct (Elsevier B. V., Amsterdam, the Netherlands) using the method of Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (Liberati et al., 2009; Moher et al., 2009). The keywords used for searching studies for meta-analysis were "chitosan, cholesterol" in all databases. The results obtained included 450 citations from Science Direct and 303 from Pubmed. These results were then filtered by title, abstract, and full text. Among them, review articles and studies of clinical tests in human models were removed. Following this, studies regarding changes in cholesterol levels after chitosan administration were collected. Ultimately, a total of 34 studies with 11 items were selected to perform a meta-analysis of the effectiveness of chitosan in reducing cholesterol in murine models.

4.2. Data analysis

Corrected standardized mean difference (Hedges' g), and 95% confidence intervals (CI) were computed between control groups and treatment. The weight of the effect size was

10

calculated using inverse-variance (Borenstein et al., 2009; Deek et al., 2011). Effect-size analysis of fixed and random effect models was used to calculate overall effect due to differences in administration period, animal strain, and the type and dosage of chitosan used in each study. Cochran's Q test was performed to assess the statistical heterogeneity of the effect size, and the ratio of true heterogeneity to total variation in observed effects was expressed by I^2 value. To confirm the heterogeneity of effect size using a mixed-effect model for the items in question, meta-ANOVA and regression analyses were also used. Finally, publication bias analysis was conducted to ensure the validity of the meta-analysis results. Statistical analysis and visualization of the results were performed using the 'meta', and 'metafor' packages in the R statistics software application (R Development Core Team, 2019 ver. 3.5.3).

5. Conclusion

The present study confirmed the effectiveness of chitosan administration on lifestyle-related diseases through meta-analysis. Based on our results, chitosan was demonstrated to be somewhat useful in improving the symptoms of lifestyle-related disease. Although the present study has some limitations, notably the limited number of animal experiments on which it is based, it may nevertheless be useful to future studies of functional foods.

Author Contributions

Cho and Choi designed the study. Ahn performed literature search and data extraction. Cho contributed to the statistical analyses. Ahn wrote the first draft of the manuscript and Cho and Choi prepared the final draft.

Acknowledgments

Conflicts of Interest

The authors declare no conflict of interest.

References

Abozaid, O. A. R.; AbdEl-hamid, O. M.; Atwa S. A. E. Hypolipidemic and anti-inflammatory effect of chitosan in experimental induced non-alcoholic fatty liver disease in rats. *Benha Veterinary Medical Journal*. **2015**, *28*, 155-165.

Ahn, S. I.; Cho, S. B.; Choi, N. J. Effect of dietary probiotics on colon length in an inflammatory bowel disease–induced murine model: A meta-analysis. *Journal of Dairy Science.* **2020,** *103*(2), 1807–1819.

Ardakani, F. E.; Karbasi, M. H. A.; Vahidi, A.; Mirjalili, N.; Eslampour, N. Effects of chitosan and Salvadora persica on blood lipids in the Wistar rat. *Medical Journal of Islamic World Academy of Sciences.* **2009***, 17*, 95-102.

Austin, P. R.; Brine, C. J.; Castle, J. E.; Zikakis, J. P. New facets of research. *Science.* **1981***, 212*(4496), 749-753.

Bahijri, S. M.; Alsheikh, L.; Ajabnoor, G.; Borai, A. Effect of supplementation with chitosan on weight, cardiometabolic, and other risk indices in Wistar rats fed normal and high-fat/high-cholesterol diets *Ad Libitum*. *Nutrition and Metabolic Insights*. **2017**, *10*, 1-8.

Van Bennekum, A. M.; Nguyen, D. V.; Schulthess, G.; Hauser, H.; Phillips, M. C. Mechanisms of cholesterol-lowering effects of dietary insoluble fibres: relationships with intestinal and hepatic cholesterol parameters. *British Journal of Nutrition.* **2005***, 94*, 331–337.

Chiang, M. T.; Yao, H. T.; Chen, H. C. Effect of dietary chitosans with different viscosity on plasma lipids and lipid peroxidation in rats fed on a diet enriched with cholesterol. *Bioscience, Biotechnology, and Biochemistry.* **2014***, 64*, 965-971.

Chiu, C. Y.; Chan, I. L.; Yang, T. H.; Liu, S. H.; Chiang, M. T. Supplementation of chitosan alleviates high-fat diet-enhanced lipogenesis in rats via adenosine monophosphate (AMP)-activated protein kinase activation and inhibition of lipogenesis-associated genes. *Journal of Agricultural and Food Chemistry.* **2015***, 63*, 2979-2988.

Chiu, C. Y.; Chang, T. C; Liu, S. H.; Chiang, M. T. The regulatory effects of fish oil and chitosan on hepatic lipogenic signals in high-fat diet-induced obese rats. *Journal of food and drug analysis*. **2017**, 25, 919-930.

Chiu, C. Y.; Yen, T. E.; Liu, S. H.; Chiang, M. T. Comparative effects and mechanisms of chitosan and its derivatives on hypercholesterolemia in high-fat diet-fed rats. *International Journal of Molecular Science.* **2020***, 21*, 92

Cho, S. B.; Lee, S. M.; Kim, E. J. Effect of different forages on growth performance, meat production and meat quality of Hanwoo steers: Meta-analysis. *Journal of Korean Society*

of Grassland and Forage Science. **2012***, 32*(2), 175-184.

Clementi, M.; Weber-Schondorfer, C. Gastro-intestinal medications, hypolipidemic agents and spasmolytics. In *Drugs during pregnancy and lactation: Treatment options and risk assessment*; Schaefer, C.; Peters, P .W. J.; Mille, R. K., Eds.; Elsevier, London, UK. 2015; pp. 93-113.

Do, A. R.; Cho, S. J.; Cho, Y. Y.; Kwon, E. Y.; Choi, J. Y.; Lee, J. H.; Han, Y.; Kim, Y. S.; Piao, Z.; Shin, Y. C.; Choi, MS. Antiobesity effects of short-chain chitosan in diet-induced obese mice. *Journal of Medicinal Food.* **2018***, 21*, 927-934.

Dehghan-Kooshkghazi, M.; Mathers, J. C. Starch digestion, large bowel fermentation and intestinal mucosal cell proliferation in rats treated with the a-glucosidase inhibitor acarbose. *British Journal of Nutrition.* **2004***, 91*, 357–365.

Egger, M. G.; Davey S.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal.* **1997***, 315*, 629–634.

Fleiss, J. L. Analysis of data from multiclinic trials. *Controlled Clinical Trials.* **1986***, 7*(4), 267-275.

Fried, S. K.; Bunkin, D. A.; Greenberg, A. S. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *The Journal of Clinical Endocrinology and Metabolism.* **1998**, *83*(3), 847-850.

Furda, I. Interaction of dietary fiber with lipids-mechanistic theories and their limitations. In *New developments in dietary fiber*; Furda, I.; Brine, C. J., Eds.; Plenum Press, New York, USA, 1990; pp. 67-82.

Gallaher, S. M.; Munion, J.; Hesslink, R. Jr.; Wise, J.; Gallaher, D. D. Cholesterol reduction by glucomannan and chitosan is mediated by changes in cholesterol absorption and bile acid and fat excretion in rats. *Journal of Nutrition.* **2000***, 130*(11), 2753-2759.

Gordon, T.; Castelli, W. P.; Dawber, T. R. Lipoprotein, cardiovascular disease and death, the Framingham study. *Archives of Internal Medicine.* **1981***, 141*, 1128-1135.

Greenland, S.; O' Rourke, K. Meta-Analysis. In *Modern Epidemiology,* 3rd ed.; Rothman, K. J.; Greenland, S.; Lash, T. L., Eds.; Lippincott Williams & Wilkins, Philadelphia, USA, 2008; pp. 652-682.

Grundy, S. M.; Cleeman, J. I.; Daniels, S. R.; Donato, K. A.; Eckel, R. H.; Franklin, B. A.; Gordon, D. J.; Krauss R. M.; Savage, P. J.; Smith Jr, S. C.; Spertus, J. A.; Costa, F. Diagnosis and management of the metabolic syndrome. *Circulation.* **2005***, 112*, 2735-2752.

Han, L. K.; Kimura, Y.; Okuda, H. Reduction in fat storage during chitin-chitosan treatment in mice fed a high-fat diet. *International Journal of Obesity.* **1999***, 23*, 174-179.

Hanefeld, M. Cardiovascular benefits and safety profile of acarbose therapy in prediabetes and established type 2 diabetes. *Cardiovascular Diabetology.* **2007***, 6*, 20.

Higgins, J.; Thompson, S.; Deeks, J.; Altman, D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *Journal of Health Services Research & Policy.* **2002***, 7*(1), 51-61.

Higgins, J. P. T.; Thompson, S. G.; Deeks, J. J.; Altman, D. G. Measuring inconsistency in meta-analyses. *British Medical Journal.* **2003***, 327*, 557-560.

Hsieh, Y. L.; Yao, H. T.; Cheng, R. S.; Chiang, M. T. ; Chitosan reduces plasma adipocytokines

and lipid accumulation in liver and adipose tissues and ameliorates insulin resistance in diabetic rats. *Journal of Medicinal food.* **2012***, 15*, 453-460.

Jennings, C. D.; Boleyn, K.; Bridges, S. R.; Wood, P. J.; Anderson, J. W. A comparison of the lipid-lowering and intestinal morphological effects of cholestyramine, chitosan, and oat gum in rats. *Experimental Biology & Medicine*. **1988**, *189*, 13-20.

Jeon, Y. J.; Kim, S. K. Effect of antimicrobial activity by chitosan oligosaccharides N-conjugated with asparagine. *Microbial Biotechnology.* **2001***, 11*, 281-286.

Jeon, Y. J.; Kim, S. K. Potential immuno-stimulating effect of antitumoral fraction of chitosan oligosaccharides. *Journal of Chitin and Chitosan.* **2001**, *6*, 163-167.

Jo, S. H.; Ha, K. S.; Moon, K. S.; Kim, J. G.; Oh, C. G.; Kim, Y. C.; Apostolidis, E.; Kwon, Y. I. Molecular weight dependent glucose lowering effect of low molecular weight chitosan oligosaccharide (GO2KA1) on postprandial blood glucose level in SD rats model. *International Journal of Molecular Sciences.* **2013***, 14*(7), 14214–14224

Johnson, I. T.; Gee, J. M. Effect of gel forming gums in the intestinal unstirred layer and sugar transport *in vitro*. *Gut.* **1981***, 22*, 398-403.

Jung, E. Y.; Hong, Y. H.; Chang, U. J.; Suh, H. J. Anti-obese effects of chitosan and psyllium husk containing vitamin C in Sprague-Dawley (SD) rats fed a high fat diet. *Progress in Nutrition.* **2016***, 18,* 152-160.

Kanauchi, O.; Deuchi, K.; Imasato, Y.; Shizukuishi, M.; Kobayashi, E. Mechanism for the inhibition of fat digestion by chitosan and for the synergistic effect of ascorbate. *Bioscience, Biotechnology, and Biochemistry*. **1995**, *59*(5), 786-790.

Kim, J. G.; Jo, S. H.; Ha, K. S.; Kim, S. C.; Kim, Y. C.; Apostolidis, E.; Kwon, Y. I. Effect of long-term supplementation of low molecular weight chitosan oligosaccharide (GO2KA1) on fasting blood glucose and HbA1c in db/db mice model and elucidation of mechanism of action. *BMC Complementary and Alternative Medicine*. **2014**, *14*, 272-278.

Kim, J. N.; Chang, I. Y.; Kim, H. I.; Yoon, S. P. Long-term effects of chitosan oligosaccharide in streptozotocin-induced diabetic rats. *Islets*. **2009**, *1*, 111-116.

Kim. M. S.; You, H. J.; You, M. K.; Kim, N. S.; Shim, B. S.; Kim, H. M. Inhibitory effect of water-soluble chitosan on TNF-alpha and Il-8 secretion from HMC-1 cells. *Immunopharmacology and Immunotoxicology*. **2004**, *26*, 401-409, 2004.

Knorr, D. Recovery and utilization of chitin and chitosan in food processing waste management. *Food Technology*. **1991**, *44*, 114-155.

Koide, S. S. Chitin-chitosan: properties, benefits, and risks. *Nutrition Research*. **1998**, *18*, 1091-1101.

Kumar, S. G.; Rahman, M. A.; Lee, S. H.; Hwang, H. S.; Kim, H. A.; Yun, J. W. Plasma proteome analysis for anti-obesity and anti-diabetic potentials of chitosan oligosaccharides in *ob/ob* mice. *Proteomics*. **2009**, *9*, 2149–2162.

Krentz, A.; Bailey, C. Oral antidiabetic agents. *Drugs*. **2004**, *65*(3), 385–411.

Lawrence, T.; Willoughby, D. A.; Gilroy, D. W. Anti-inflammatory lipid mediators and insights into the resolution of inflammation. *Nature Reviews Immunology*. **2002**, *2*, 787-795.

Lee, J. M.; Cho, W. K.; Park, H. J. Effects of chitosan treated with enzymatic methods on glucose and lipid metabolism in rat. *Korean Journal of Nutrition*. **1998**, *31*, 1112-1120.

Liberati, A.; Altman, D. G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P. C.; Loannidis, J. P. A.; Clarke, M.; Devereraux, P. J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *BMJ*. **2009***, 339*, b2700.

Liu, S. H.; Cai, F. Y.; Chiang, M. T. Long-term feeding of chitosan ameliorates glucose and lipid metabolismin a high-fructose-diet-impaired rat model of glucose tolerance. *Marine Drugs*. **2015***, 13*, 7302-7313.

Liu, S. H.; Chiu, C. Y.; Shi, C. M.; Chiang, M. T. Functional comparison of high and low molecular weight chitosan on lipid metabolism and signals in high-fat diet-fed rats. *Marine Drugs*. **2018***, 16*, 251.

Liu, S. H.; He, S. P.; Chiang, M. T. Effects of long-term feeding of chitosan on postprandial lipid responses and lipid metabolism in a high-sucrose-diet-impaired glucose-tolerant rat model. *Journal of Agricultural and Food Chemistry*. **2012***, 60*, 4306-4313.

Lin, W. W.; Karin, M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *Journal of Clinical Investigation*. **2017**, *117*, 1175-1183.

Mohamed-Ali V.; Goodrick S.; Rawesh A.; Katz D. R.; Miles J. M.; Yudkin J. S.; Klein S.; Coppack S. W. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, *in vivo*. *The Journal of Clinical Endocrinology and Metabolism*. **1997**, *82*(12), 4196-4200.

Moher, D. A.; Liberati, A.; Tetzlaff, J.; Altman, D. G.; Group, P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. **2009**, *6*:e1000097.

Moon, M. S.; Lee, M. S.; Kim, C. T.; Kim, Y. Dietary chitosan enhances hepatic CYP7A1 activity and reduces plasma and liver cholesterol concentrations in diet-induced hypercholesterolemia in rats. *Nutrition Research and Practice.* **2007***, 1*, 175-179.

Nauss, J. L.; Thompson, J. L.; Nagyvary, J. The binding of micellar lipids to chitosan. *Lipids.* **1983***, 18,* 714–719.

Park, J. H.; Hong, E. K.; Ahn, J.; Kwak, H. S. Properties of nanopowdered chitosan and its cholesterol lowering effect in rats. *Food Science and Biotechnology.* **2010***, 19*, 1457-1462.

Petitti, D. B.. Approaches to heterogeneity in meta-analysis. *Statistics in Medicine.* **2001**, *20*, 3625-3633.

Prabu, K.; Natarajan, E. Antihyperglycemic effect of chitosan of urophthalmus vigil in streptozotocin induced diabetic rats. *International Journal of Pharmaceutical Science and Research.* **2013***, 4*(1), 352-359.

Puls, W.; Keup, U.; Krause, H. P.; Thomas, G.; Hoffmeister, F. Glucosidase inhibition. A new approach to the treatment of diabetes, obesity, and hyperlipoproteinaemia. *Naturwissenschaften.* **1977**, *64*, 36–537.

Razdan, A.; Pettersson, D. Effect of chitosan on nutrient digestibility and plasma lipid concentration in broiler chickens. *British Journal of Nutrition.* **1994***, 72*, 277-288.

Sivakumar, R.; Rajesh, R.; Buddhan, S.; Jeyakumar, R.; Rajaprabhu, D.; Ganersan, B.; Anadan, R. Antilipidemic effect of chitosan against experimentally induced myocardial infarction in rats. *Journal of Cell and Animal Biology.* **2007**, *1*, 71-77.

Seo, S. B.; Jeong, H. J.; Chung, H. S.; Lee, J. D.; You, Y. O.; Kajiuchi, T.; Kim, H. M. Inhibitory

effect of high molecular weight water-soluble chitosan on hypoxia-induced inflammatory cytokine production. *Biological and Pharmaceutical Bulletin.* **2003***, 26*, 717-721.

Shang, W.; Si, X.; Zhou, Z.; Wanga, J.; Strappe, P.; Blanchard, C. Studies on the unique properties of resistant starch and chitooligosaccharide complexes for reducing high-fat diet-induced obesity and dyslipidemia in rats. *Journal of Functional Foods.* **2017***, 38*, 20-27.

Si, X.; Strappe, P.; Blanchard, C.; Zhou, Z. Enhanced anti-obesity effects of complex of resistant starch and chitosan in high fat diet fed rats. *Carbohydrate Polymers.* **2017***, 157*, 834–841.

Sugano, M.; Fujikawa, T.; Hiratsuji, Y.; Hasegawa, Y. Hypocholesterolemic effects of chitosan in cholesterol-fed rats. *Nutrition Reports International.* **1978***, 18*, 531-536.

Tao, Y.; Zhang, H.; Gao, B.; Guo, J.; Hu, Y.; Su, Z. Water-soluble chitosan nanoparticles inhibit hypercholesterolemia induced by feeding a high-fat diet in male Sprague-Dawley rats. *Journal of Nanomaterials.* **2011**, 1-5.

Thayer, J. F.; Yamamoto, S. S.; Brosschot, J. F. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology.* **2010**, *141*, 122-131.

Tufanaru, C.; Munn, Z.; Aromataris, E.; Campbell, J.; Hopp, L. Systematic reviews of effectiveness. In *The Joanna Briggs Institute Reviewer's Manual*; Aromataris E.; Munn, Z., Eds.; 2017. Available from https://reviewersmanual.joannabriggs.org/

Vahouny, G. V.; Satchihanandam, S.; Cassidy, M. M.; Lightfoot, F. B.; Furda, I. Comparative effects of chitosan and cholestyramine on lymphatic absorption of lipids in the rat. *The American Journal of Clinical Nutrition*. **1983**, *38*, 278-284.

Wang, D.; Han, J.; Yu, Y.; Li, X.; Wang, Y. Chitosan oligosaccharide decreases very-low-density lipoprotein triglyceride and increases high-density lipoprotein cholesterol in high-fat-diet-fed rats. *Experimental Biology and Medicine.* **2011**, *236*, 1064–1069.

Wang, Z.; Zhang, F.; Yan, Y.; Zhang, Z.; Wang, L.; Qin, C. Lipid-lowering activities of chitosan and its quaternary ammonium salt for the hyperlipidemia rats induced by high-fat diets. *International Journal of Biological Macromolecules.* **2019**, *132*, 922-928.

Yao, H. T.; Chiang, M. T. Effect of chitosan on plasma lipids, hepatic lipids, and fecal bile acid in hamsters. *Journal of Food and Drug Analysis.* **2006**, *14*, 183-189.

Yermak, I. M.; Davidova, V. N.; Gorvach, V. I.; Luk'yanov, P. A.; Solov'eva, T. F.; Ulmer, A. J.; Buwitt-Beckmann, U.; Rietschel, E. T.; Ovodov, Y. S. Forming and immunological properties of some lipopolysaccharide-chitosan complexes. **2005**, *Biochimie 88*, 23-30.

Yoon, H. J.; Moon, M. E.; Park, H. S.; Im, S. Y.; Kim, Y. H. Chitosan oligosaccharide (COS) inhibits LPS-induced inflammatory effects in RAW 264.7 macrophage cells. *Biochemical and Biophysical Research Communications.* **2007**, *358*(3), 954-959.

Zacour, A. C.; Silva, M. E.; Cecon, P. R.; Bambirra, E. A.; Vieira, E. C. Effect of dietary chitin on cholesterol absorption and metabolism in rats. *Journal of Nutritional Science and Vitaminology.* **1992**, *38*, 609-613.

Zhang, H. L.; Tao, Y.; Guo, J.; Hu, Y. M.; Su, Z. Q. Hypolipidemic effects of chitosan nanoparticles in hyperlipidemia rats induced by high fat diet. *International Immunopharmacology.* **2011**, *11*, 457-461.

Zhang, H. L.; Zhong, X. B.; Tao, Y.; Wu, S. H.; Su, Z. Q. Effects of chitosan and water-soluble chitosan micro- and nanoparticles in obese rats fed a high-fat diet. International *Journal of*

Nanomedicine. **2012***, 7*, 4069-4076.

Zhang, J.; Zhang, W.; Mamadouba, B.; Xia, W. A comparative study on hypolipidemic activities of high and low molecular weight chitosan in rats. *International Journal of Biological Macromolecules.* **2012***, 51*, 504-508.

Zhang, J. M.; An, J. Cytokines, inflammation and pain. *International Anesthesiology Clinics.* **2007***, 45*, 27-37.

Zhang W.; Xia, W. Effect of media milling on lipid-lowering and antioxidant activities of chitosan. *International Journal of Biological Macromolecules.* **2015***, 72*, 1402-1405.

Zhou, G. D.; Li, M. R.; Zhang, J.; Pan, D.; Zhao, S. X.; Yang, J. F.; Yu, J.; Zhao, J. M. Chitosan ameliorates the severity of steatohepatitis induced by high fat diet in rats. *Scandinavian Journal of Gastroenterolog*y. **2008**, l*43*, 1371-1377.

Zhu, J.; Zhang, Y.; Wu, G.; Xiao, Z.; Zhou, H.; Yu, X. Inhibitory effects of oligochitosan on TNF-α, IL-1β and nitric oxide production in lipopolysaccharide-induced RAW264.7 cells. *Molecular Medicine Reports.* **2015***, 11*, 729-733.

Ziamajidi, N.; Nasiri, A.; Abbasalipourkabir, R.; Sadeghi Moheb, S. Effects of garlic extract on TNF-alpha expression and oxidative stress status in the kidneys of rats with STZ + nicotinamide-induced diabetes. *Pharmaceutical Biology.* **2017***, 55*(1), 526–531.

Zong, C.; Yu, Y.; Song, G.; Luo, T.; Li, L.; Wang, X.; Qin, S. Chitosan oligosaccharides promote reverse cholesterol transport and expression of scavenger receptor BI and CYP7A1 in mice. *Experimental Biology and Medicine.* **2012***, 237*, 194-200.

Figure legends

Figure 1. Funnel plot to evaluate publication bias. Blood TC (A); blood TG (B); LDL-C (C); HDL-C (D); liver TC; liver TG (F); fecal TC (G); body weight (H)

Figure 2. Schematic representation of cholesterol adsorption of chitosan in gastro-intestinal tracts

1   Table 1. Studies used in data set and their information for meta-analysis

Authors	Animal (strain)	n	Week	Experimental diet	Analytical items[1]
Abozaid et al. (2015)	Rat (white Albino)	10	6	High fat	TC*, TG*, LDL-C*, HDL-C*, TNF-α*
Bahijri et al. (2017)	Rat (Wistar)	10	12	High fat	TC*, TG*, LDL-C*, HDL-C*
Chiu et al. (2015)	Rat (Sprague−Dawley)	8	7	High fat	TC*, TG*, TC‡, TG‡
Liu et al. (2018)	Rat (Sprague−Dawley)	8	8	High fat	TC*, TG*, LDL-C*, HDL-C*, TNF-α*
Park et al. (2010)	Rat (Sprague−Dawley)	8	8	High fat	TC*, TG*, LDL-C*, HDL-C*, TC†, TG†, TC‡
Sivakumar et al. (2007)	Rat (Wistar)	6	8.5	High fat	TC*, TG*, LDL-C*, HDL-C*
Sugano et al. (1978)	Rat (Wistar)	6	2.8	High fat	TC*, TG*, TC†, TG†, TC‡
Tao et al. (2001)	Rat (Sprague−Dawley)	8	4	High fat	TC*, TG*, LDL-C*, HDL-C*
Zacour et al. (1992)	Rat (Wistar)	6	6	High fat	TC*, TG*, TC†, TG†, TC‡, TG‡
Yao and Chiang (2006)	Hamster	9	8	High fat	TC*, TG*, LDL-C*, HDL-C*, TC†, TG†, TC‡
Moon et al. (2007)	Rat (Sprague−Dawley)	8	4	High fat	TC*, TG*, LDL-C*, HDL-C*, TC†
Chiu et al. (2017)	Rat (Sprague−Dawley)	8	5	High fat	TC*, TG*, HDL-C*, TC‡, TG‡
Liu et al. (2015)	Rat (Sprague−Dawley)	8	21	High fructose	TC*, TG*, HDL-C*, TC†, TG†, TC‡, TG‡

Ardakani et al. (2009)	Rat (Wistar)	5	2	High fat	TC*, TG*, LDL-C*, HDL-C*
Jung et al. (2016)	Rat (Sprague−Dawley)	8	6	High fat	TC*, TG*, LDL-C*, HDL-C*
Hsieh et al. (2012)	Rat (Sprague−Dawley)	9.5	10	High fat	TC†, TG†, TNF-α*
Han et al. (1999)	Mouse (ICR)	13	9	High fat	TC*, TG, TC†, TG†, body weight
Chiang et al. (2000)	Rat (Sprague−Dawley)	6	4	Normal diet + cellulose 5%	TC*, LDL-C*, HDL-C*, TC†, TG†, TC‡, TG‡
Shang et al. (2007)	Rat (Sprague−Dawley)	8	6	High fat	TC*, TG*, LDL-C*, HDL-C*, body weight
Zhang et al. (2010)	Rat (Sprague−Dawley)	8	4	High fat	TC*, TG*, LDL-C*, HDL-C*
van Bennekum et al. (2005)	Mouse (C57BL/6)	6	3	High fat	TC*, TC†
Zhou et al. (2008)	Rat (Sprague−Dawley)	12	8	High fat	TC*, TG*, LDL-C*, HDL-C*, TNF-α*, glucose*
Kumar et al. (2009)	Mouse (C57BL/6)	6	4	High fat	TC*, TG*
Kim et al. (2009)	Rat (Sprague−Dawley)	5	8	High fat	TC*, body weight
Zong et al. (2012)	Mouse (C57BL/6)	6	6	High fat	TC*, TG*, LDL-C*, HDL-C*, body weight,
Liu et al. (2012)	Rat (Sprague−Dawley)	9	16	High sucrose	TC*, TG*, HDL-C*, TNF-α*, glucose*
Zhang et al. (2012a)	Rat (Sprague−Dawley)	8	8	High fat	TC*, TG*, LDL-C*, HDL-C*, TC†, TG†

25

Zhang et al. (2012b)	Rat (Sprague−Dawley)	10	4	High fat	TC*, TG*, LDL-C*, HDL-C*
Zhang and Xia (2015)	Rat (Sprague−Dawley)	8	8	High fat	TC*, TG*, LDL-C*, HDL-C*, TC[†], TG[†], TC[‡], body weight
Si et al. (2017)	Rat (Wistar)	8	6	High fat	TC*, TG*, LDL-C*, HDL-C*, body weight, glucose*
Do et al. (2018)	Mouse (C57BL/6)	10	12	High fat	TC*, TG*, HDL-C*, TC[†], TG[†], TC[‡], TG[‡], body weight
Wang et al. (2019)	Rat (Sprague−Dawley)	8	4.2	High fat	TC*, TG*, LDL-C*, HDL-C*, TC[†], TG[†], TC[‡], body weight
Chiu et al. (2020)	Rat (Sprague−Dawley)	6	8	High fat	TC*, TC[†], TC[‡], TNF-α*
Wang et al. (2011)	Rat (Wistar)	8	3	High fat	TG*, LDL-C*, HDL-C*

[1]TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TNF-α, tumor necrosis factor-α; *, blood; [†], liver; [‡], feces

12   Table 2. Effect size of chitosan administration on hyperlipidemia in murine model

Items	df	Fixed effect model		Random effect model		Heterogeneity		
		ES[1]	*p*-value	ES	*p*-value	Q (*p*-value)	I^2 (%)	τ^2
Total cholesterol (blood)	65	-1.5457	< 0.0001	-2.2248	< 0.0001	376.43 (< 0.0001)	82.7	2.1388
Triglyceride (blood)	63	-0.5852	< 0.0001	-1.2366	< 0.0001	525.93 (< 0.0001)	88.0	2.6610
LDL-cholesterol (blood)	46	-1.6121	< 0.0001	-2.5212	< 0.0001	294.88 (< 0.0001)	84.4	2.5182
HDL-cholesterol (blood)	49	0.1318	0.1363	0.1532	0.5704	431.89 (< 0.0001)	88.7	3.0718
Total cholesterol (liver)	30	-2.3101	< 0.0001	-3.3734	< 0.0001	187.28 (< 0.0001)	84.0	3.2403
Triglyceride (liver)	22	-2.1172	< 0.0001	-3.2648	< 0.0001	172.75 (< 0.0001)	87.3	3.8731
Total cholesterol (feces)	22	1.8491	< 0.0001	2.6038	< 0.0001	113.25 (< 0.0001)	80.6	2.2198
Triglyceride (feces)	9	2.0168	< 0.0001	2.4130	< 0.0001	35.30 (< 0.0001)	74.5	1.5050
TNF-α	12	-1.4885	< 0.0001	-1.8355	< 0.0001	66.72 (< 0.0001)	82.0	1.8174
Body weight	21	-1.5974	< 0.0001	-2.4442	< 0.0001	162.18 (< 0.0001)	87.1	3.1836
Glucose (blood)	12	-0.7512	< 0.0001	-0.8958	0.0096	61.64 (< 0.0001)	80.5	1.2356

13   [1]ES: effect size

14   Table 3. Meta-ANOVA analysis of effect of chitosan type on biological indices

Biological index[1]	Analysis item[2]	k[3]	Fixed effect model			Random effect model			Q[6]	τ^{2}[7]	I^{2}[8]	Q_b[9]	df[10]	p
			SMD[4]	95% -CI[5]		SMD	95% -CI							
				lower	upper		lower	upper						
TC (blood)	CTS	42	-1.5720	-1.7639	-1.3801	-2.0640	-2.5645	-1.5635	194.29	2.2266	78.9			
	WSC	17	-1.5434	-1.9066	-1.1801	-2.7620	-3.6088	-1.9153	145.47	2.2266	89.0			
	RS	2	-1.7624	-2.6836	-0.8412	-2.3197	-4.6315	-0.0080	6.88	2.2266	85.5			
	CE	1	-2.1859	-3.7413	-0.6305	-2.1859	-5.4984	1.1266	0.00	-	-	12.60	7	0.0826
	CTS+RS	1	-8.9998	-12.7228	-5.2769	-8.9998	-13.7341	-4.2655	0.00	-	-			
	WSC+RS	1	-1.4835	-4.6243	1.6572	-1.4835	-4.6243	1.6572	0.00	-	-			
	CTS+VitC	1	0.2823	-0.7041	1.2688	0.2823	-2.8042	3.3688	0.00	-	-			
	CSR	1	-1.9182	-3.3870	-0.4494	-1.9182	-5.1910	1.3545	0.00	-	-			
TG (blood)	CTS	39	-0.4142	-0.6035	-0.2249	-1.0874	-1.6614	-0.5135	378.70	2.8583	90.0			
	WSC	17	-1.1778	-1.4773	-0.8782	-1.9030	-2.7835	-1.0224	86.48	2.8583	81.5			
	RS	2	-0.8491	-1.6483	-0.0499	-1.1971	-3.6866	1.2924	7.64	2.8583	86.9			
	CE	1	1.1106	0.0996	2.1216	1.1106	-2.3538	4.5750	0.00	-	-	5.50	6	0.4819
	CTS+RS	1	-3.4066	-5.0825	-1.7307	-3.4066	-7.1199	0.3067	0.00	-	-			
	WSC+RS	1	-1.4338	-2.5685	-0.2990	-1.4338	-4.9363	2.0688	0.00	-	-			
	CTS+VitC	1	-0.8606	-1.8990	0.1778	-0.8606	-4.3331	2.6119	0.00	-	-			
LDL-C (blood)	CTS	28	-2.1800	-2.4471	-1.9129	-2.8041	-3.4238	-2.1843	100.39	1.9848	73.1			
	WSC	13	-1.6760	-2.0564	-1.2956	-2.8831	-3.8113	-1.9550	100.21	1.9848	88.0	6.27	3	0.0990
	RS	2	-0.2492	-0.9457	0.4474	-0.2492	-2.3222	1.8238	0.00	1.9848	0.0			
	CTS+RS	2	-1.6799	-2.5327	-0.8270	-1.7721	-3.9089	0.3647	1.49	1.9848	32.9			

28

HDL-C (blood)	CTS	36	0.1332	-0.0704	0.3368	0.3816	-0.2696	1.0329	315.19	3.3880	88.9			
	WSC	10	-0.0158	-0.4449	0.4132	-0.7968	-2.0465	0.4528	107.00	3.3880	91.6			
	RS	2	-0.1120	-0.8081	0.5842	-0.1134	-2.7577	2.5308	0.34	3.3880	0.0	3.63	4	0.4585
	CTS+RS	1	1.9999	0.7360	3.2638	1.9999	-1.8227	5.8225	0.00	-	-			
	WSC+RS	1	0.2293	-0.7549	1.2135	0.2293	-3.5102	3.9688	0.00	-	-			
TC (liver)	CTS	26	-2.5523	-2.8603	-2.2442	-3.6571	-4.4528	-2.8614	157.12	3.2800	84.1			
	WSC	3	-1.0529	-1.7573	-0.3485	-1.5068	-3.6972	0.6837	11.05	3.2800	81.9	4.50	3	0.2122
	CE	1	-1.5873	-2.9588	-0.2158	-1.5873	-5.3927	2.2181	0.00	-	-			
	CSR	1	-4.7470	-7.3259	-2.1682	-4.7470	-9.1346	-0.3595	0.00	-	-			
TG (liver)	CTS	19	-1.9028	-2.2234	-1.5823	-3.0600	-4.0045	-2.1154	153.33	3.5904	88.3	0.91	1	0.3410
	WSC	4	-3.9955	-4.9445	-3.0466	-4.1792	-6.2803	-2.0781	2.65	3.5904	0.0			
TC (feces)	CTS	20	1.8847	1.5660	2.2034	2.6479	1.8759	3.4200	97.07	2.3783	80.4	0.04	1	0.8341
	WSC	3	1.6188	0.8072	2.4304	2.4194	0.4258	4.4131	15.82	2.3783	87.4			
Body weight	CTS	11	-2.4795	-2.9132	-2.0458	-3.4586	-4.5418	-2.3755	78.81	2.5667	87.3			
	WSC	7	-0.5100	-0.9616	-0.0584	-0.5950	-1.8669	0.6769	22.98	2.5667	73.9			
	RS	2	-1.7624	-2.6836	-0.8412	-2.3356	-4.7858	0.1147	6.88	2.5667	85.5	18.75	4	0.0009
	CTS+RS	1	-8.9998	-12.7228	-5.2769	-8.9998	-13.8702	-4.1295	0.00	-	-			
	WSC+RS	1	-1.4835	-2.6285	-0.3386	-1.4835	-4.8258	1.8588	0.00	-	-			
TNF-α	CTS	12	-1.6953	-2.0508	-1.3398	-2.0430	-2.8184	-1.2676	49.88	1.4116	77.9	19.84	3	0.0002
	WSC	1	0.9843	-0.2451	2.2137	0.9843	-1.6489	3.6175	0.00	-	-			
Glucose (blood)	CTS	10	-0.7573	-1.0898	-0.4247	-0.9044	-1.6869	-0.1218	48.68	1.2809	81.5			
	RS	1	-1.6688	-2.8537	-0.4840	-1.6688	-4.1837	0.8460	0.00	-	-			
	CTS+RS	1	-1.7693	-2.9772	-0.5615	-1.7693	-4.2951	0.7564	0.00	-	-	2.49	3	0.4765
	CTS+VitC	1	0.7144	-0.3062	1.7350	0.7144	-1.7274	3.1562	0.00	-	-			

15   [1]TC, total cholesterol; TG, triglyceride, LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein, TNF-α; Tumor necrosis factor alpha

16   [2]CTS, chitosan; WSC, water-soluble chitosan; RS, resistant starch; CE, cellulose; CTS+RS, chitosan and resistant starch; WSC+RS, water-

17   soluble chitosan and resistant starch; CTS+VitC, chitosan and vitamin C; CSR, cholestyramine

18   [3]k: number of treatments

19   [4]SMD: standardized mean difference

20   [5]CI: confidence interval

21   [6]Q: chi-squared statistic

22   [7]τ^2: true heterogeneity

23   [8]I^2: Higgin's I^2 statistic

24   [9]Q_b: Q statistics between groups

25   [10]df: degrees of freedom of Q statistic

26

27

30

28   Table 4. Meta-ANOVA analysis of effect of chitosan administration period on biological indices

Item[1]	Administration period (week)	K[2]	Fixed effect model			Random effect model			Q[5]	τ^{2} [6]	I^{2} [7]	Q_b [8]	Df[9]	p
			SMD[3]	95% -CI[4]		SMD	95% -CI							
				lower	upper		lower	upper						
TC (blood)	2	1	-2.4519	-4.3072	-0.5966	-2.4519	-5.6070	0.7668	0.00	-	-			
	2.8	1	-5.4530	-8.3456	-2.5605	-5.4530	-9.3626	-1.5435	0.00	-	-			
	3	3	-1.7388	-2.5626	-0.9149	-1.7849	3.5161	-0.0536	0.84	1.8009	0.0			
	4	15	-2.4145	-2.7809	-2.0482	3.0386	-3.8429	-2.2343	58.25	1.8009	76.0			
	4.2	4	-1.4345	-2.0713	-0.7978	-2.1531	-3.6612	-0.6451	19.86	1.8009	84.9			
	5	1	-2.1630	-3.4689	-0.8570	-2.1630	-5.0996	0.7736	0.00	-	-	31.94	13	0.0025
	6	13	-0.8035	-1.1424	-0.4645	-1.3554	-2.1863	-0.5246	73.20	1.8009	83.6			
	7	3	0.1396	-0.4290	0.7082	0.1408	-1.4807	1.7624	0.48	1.8009	0.0			
	8	13	-1.9919	-2.3823	-1.6016	-2.4673	-3.3262	-1.6083	45.48	1.8009	73.6			
	8.5	1	-2.6715	-4.3982	-0.9449	-2.6715	-5.8178	0.4748	0.00	-	-			
	9	3	-3.9353	-4.8325	-3.0381	-5.3277	-7.2274	-3.4280	26.07	1.8009	92.3			
	12	4	-1.1933	-1.8028	-0.5839	-1.8238	-3.3133	-0.3343	31.08	1.8009	90.3			
	16	3	-1.1877	-1.7836	-0.5919	-1.2240	-2.8565	0.4085	1.48	1.8009	0.0			
	21	1	-1.2794	-2.3845	-0.1744	-1.2794	-4.1324	1.5735	0.00	-	-			
TG (blood)	2	1	-1.7652	-3.3540	-0.1764	-1.7652	-4.6864	1.1560	0.00	-	-			
	2.8	1	1.5689	0.2025	2.9353	1.5689	-1.2375	4.3754	0.00	-	-			
	3	2	-1.1789	-1.9477	-0.4101	-1.1794	-3.0756	0.7168	0.01	1.5643	0.0	96.55	13	< 0.0001
	4	15	-0.6150	-0.9114	-0.3186	-1.1423	-1.8601	-0.4246	115.66	1.5643	87.9			
	4.2	4	-3.0564	-3.8949	-2.2179	-3.6529	-5.1879	-2.1179	12.50	1.5643	76.0			

	5	1	-0.5418	-1.5454	0.4617	-0.5418	-3.1906	2.1070	0.00	-	-		
	6	13	-0.9085	-1.2282	-0.5889	-1.0837	-1.8397	-0.3276	38.28	1.5643	68.6		
	7	3	1.1330	0.5098	1.7563	1.1336	-0.4129	2.6800	0.02	1.5643	0.0		
	8	10	-0.8028	-1.1722	-0.4333	-1.3193	-2.1969	-0.4417	68.52	1.5643	86.9		
	8.5	1	-2.5453	-4.2258	-0.8647	-2.5453	-5.5173	0.4268	0.00	-	-		
	9	3	-9.3202	-10.9958	-7.6445	-9.5824	-11.8082	-7.3566	4.23	1.5643	52.7		
	12	3	-1.6964	-2.3414	-1.0515	-2.0228	-3.5934	-0.4521	10.45	1.5643	80.9		
	16	4	1.3087	0.7842	1.8333	1.3374	0.0031	2.6716	1.33	1.5643	0.0		
	21	1	1.3630	0.2421	2.4838	1.3630	-1.3324	4.0584	0.00	-	-		
	2	1	-1.7162	-3.2878	-0.1445	-1.7162	-4.3664	0.9341	0.00	-	-		
	3	2	-0.2574	-0.9554	0.4407	-0.2590	-1.9216	1.4036	0.18	1.1854	0.0		
	4	15	-2.2993	-2.6446	-1.9539	-2.5700	-3.2315	-1.9085	33.05	1.1854	57.6		
LDL-C (blood)	4.2	4	-11.5502	-13.9253	-9.1751	-11.6010	-14.2147	-8.9872	1.53	1.1854	0.0	59.48	7	< 0.0001
	6	11	-1.4658	-1.8446	-1.0870	-1.7983	-2.5618	-1.0348	32.11	1.1854	68.9		
	8	10	-1.7590	-2.1810	-1.3371	-2.5968	-3.4802	-1.7134	60.61	1.1854	85.2		
	8.5	1	-5.2140	-7.9995	-2.4285	-5.2140	-8.7229	-1.7050	0.00	-	-		
	12	1	-2.6102	-3.8684	-1.3520	-2.6102	-5.0875	-0.1329	0.00	-	-		
	2	1	1.0239	-0.3431	2.3910	1.0239	-2.2340	4.2819	0.00	-	-		
	3	2	0.5630	-0.6456	1.7715	0.5824	-1.8350	2.9998	0.18	2.2766	0.0		
HDL-C (blood)	4	13	-2.0684	-2.4694	-1.6673	-2.9457	-3.883.7	-2.0077	106.17	2.2766	88.7	69.79	10	< 0.0001
	4.2	4	0.0038	-0.4905	0.4981	0.0015	-1.5576	1.5606	1.69	2.2766	0.0		
	5	1	0.4126	-0.5811	1.4064	0.4126	-2.7071	3.5324	0.00	-	-		
	6	13	0.5061	0.1888	0.8233	0.9245	0.0276	1.8213	63.04	2.2766	81.0		

	8	8	1.3101	0.9108	1.7093	1.5747	0.4469	2.7025	21.96	2.2766	68.1		
	8.5	1	5.6757	2.6829	8.6686	5.6757	1.4683	9.8832	0.00	-	-		
	12	3	0.2234	-0.6859	1.1328	4.0812	1.8229	6.3396	66.29	2.2766	97.0		
	16	3	0.4824	-0.1859	1.1506	0.4850	-1.3486	2.3185	0.14	2.2766	0.0		
	21	1	0.6661	-0.3493	1.6815	0.6661	-2.4607	3.7928	0.00	-	-		
TC (liver)	2.8	1	-9.3712	-14.0837	-4.6586	-9.3712	-14.5605	-4.1818	0.00	-	-		
	3	3	-2.2552	-3.2123	-1.2980	-2.5488	-4.1731	-0.9244	4.50	1.2291	55.6		
	4	4	-1.1782	-1.8149	-0.5415	-1.6315	-2.9484	-0.3146	11.98	1.2291	75.0		
	4.2	4	-1.4115	-2.0064	-0.8165	-1.6940	-2.9526	-0.4353	9.42	1.2291	68.1		
	6	1	-1.6407	-3.0270	-0.2543	-1.6407	-4.2182	0.9368	0.00	-	-	62.17	9	< 0.0001
	8	10	-2.4940	-2.9903	-1.9978	-2.9111	-3.7901	-2.0320	32.45	1.2291	72.3		
	9	3	-9.3634	-11.0438	-7.6830	-9.5728	-11.6968	-7.4488	3.86	1.2291	48.2		
	10	2	-2.7055	-3.6429	-1.7681	-2.7400	-4.5432	-0.9368	0.52	1.2291	0.0		
	12	2	-6.7401	-8.5025	-4.9776	-6.7503	-9.0902	-4.4104	0.11	1.2291	0.0		
	21	1	-3.0412	-4.6012	-1.4813	-3.0412	-5.7161	-0.3664	0.00	-	-		
TG (liver)	2.8	1	-5.1384	-7.8902	-2.3866	-5.1384	-9.5841	-0.6927	0.00	-	-		
	4	2	0.6597	-0.1879	1.5072	0.7060	-1.9059	3.3180	1.18	3.1738	15.0		
	4.2	4	-2.8029	-3.5742	-2.0316	-3.1371	-5.0651	-1.2092	6.82	3.1738	56.0		
	6	1	-3.2107	-5.1438	-1.2775	-3.2107	-7.2018	0.7804	0.00	-	-		
	8	7	-2.5754	-3.2000	-1.9508	-4.0563	-5.5980	-2.5146	47.21	3.1738	87.3	18.28	8	0.0192
	9	3	-3.3928	-4.2013	-2.5842	-4.7613	-7.0104	-2.5123	24.84	3.1738	91.9		
	10	2	-0.9960	-1.6800	-0.3120	-0.9970	-3.5590	1.5650	0.03	3.1738	0.0		
	12	2	-5.0743	-6.5083	-3.6403	-5.6019	-8.5208	-2.6830	4.14	3.1738	75.8		
	21	1	-1.8937	-3.1313	-0.6562	-1.8937	-5.5982	1.8108	0.00	-	-		

TC (feces)	2.8	1	5.3232	2.4889	8.1575	5.3232	1.3385	9.3079	0.00	-	-		
	4	2	0.5976	-0.2454	1.4405	0.6403	-1.5136	2.7943	1.26	2.0420	20.6		
	4.2	4	1.6887	0.9671	2.4103	3.0580	1.3721	4.7439	30.95	2.0420	90.3		
	5	1	1.0557	-0.0110	2.1224	1.0557	-1.9414	4.0527	0.00	-	-		
	6	1	1.7250	0.3145	3.1356	1.7250	-1.4109	4.8609	0.00	-	-	10.86	8	0.2098
	7	3	3.0554	2.1511	3.9596	3.0669	1.2132	4.9206	0.18	2.0420	0.0		
	8	8	1.5481	1.0714	2.0247	2.2101	1.0727	3.3475	33.38	2.0420	79.0		
	12	2	4.1314	2.9406	5.3221	4.1879	1.8709	6.5048	0.59	2.0420	0.0		
	21	1	5.0436	2.8049	7.2823	5.0436	1.4581	8.6292	0.00	-	-		
TG (feces)	4	2	2.0809	1.0028	3.1590	2.0809	1.0028	3.1590	0.17	0.0000	0.0		
	5	1	0.1343	-0.8472	1.1157	0.1343	-0.8472	1.1157	0.00	-	-		
	6	1	2.3328	0.7274	3.9382	2.3328	0.7274	3.9382	0.00	-	-	34.97	5	< 0.0001
	7	3	1.9419	1.2198	2.6640	1.9419	1.2198	2.6640	0.16	0.0000	0.0		
	12	2	5.2475	3.8224	6.6726	5.2475	3.8224	6.6726	0.00	0.0000	0.0		
	21	1	2.7213	1.2585	4.1841	2.7213	1.2585	4.1841	0.00	-	-		
Body weight	4.2	4	-1.7969	-2.4141	-1.1796	-1.8690	-3.7561	-0.0360	3.13	3.1917	4.1		
	6	9	-0.9479	-1.3802	-0.5155	-1.8184	-3.1069	-0.5299	56.45	3.1917	85.8		
	8	3	-1.4852	-2.2513	-0.7191	-1.8393	-4.0223	0.3436	9.29	3.1917	78.5	8.74	4	0.0679
	9	3	-3.9353	-4.8325	-3.0381	-5.6255	-7.9722	-3.2789	26.07	3.1917	92.3		
	12	3	-1.7793	-2.6526	-0.9059	-2.8871	-5.1625	-0.6117	31.84	3.1917	93.7		
TNF-α	6	1	-8.0454	-10.9625	-5.1282	-8.0454	-11.4788	-4.6119	0.00	-	-		
	8	7	-1.0126	-1.4568	-0.5683	-1.0557	-1.8732	-0.2382	27.60	0.8535	78.3	19.84	3	0.0002
	10	2	-3.4666	-4.5486	-2.3845	-3.4672	-5.1437	-1.7908	0.01	0.8535	0.0		
	16	3	-1.4696	-2.0976	-0.8416	-1.5301	-2.7528	-0.3075	2.46	0.8535	18.6		

34

	k							Q	τ^2	I^2	Q_b	df	
	6	5	-0.4178	-0.9320	0.0963	-0.4410	-1.5333	0.6513	30.43	1.2036	86.9		
	8	1	-4.5622	-6.1849	-2.9395	-4.5622	-7.2560	-1.8684	0.00	-	-		
Glucose (blood)	10	2	-1.2618	-1.9991	-0.5246	-1.2927	-2.9841	0.3987	0.83	1.2036	0.0	8.51	5	0.1304
	12	1	-0.1355	-1.0133	0.7423	-0.1355	-2.4580	2.1870	0.00	-	-		
	16	3	-0.6143	-1.1747	-0.0522	-0.6727	-2.0368	0.6914	3.57	1.2036	43.9		
	21	1	-0.8705	-1.9103	0.1692	-0.8705	-3.2590	1.5179	0.00	-	-		

29   [1]TC, total cholesterol; TG, triglyceride, LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein, TNF-α; Tumor necrosis factor alpha

30   [2]k: number of treatments

31   [3]SMD: standardized mean difference

32   [4]CI: confidence interval

33   [5]Q: chi-squared statistic

34   [6]τ^2: true heterogeneity

35   [7]I^2: Higgin's I^2 statistic

36   [8]Q_b: Q statistics between groups

37   [9]df: degrees of freedom of Q statistic

38

39   Table 5. Meta-regression analysis of effect of probiotic strains on inflammatory bowel disease

Item	Intercept[1]		Estimate	SE	*p*-value[2]	ci. lb	ci. ub	R^2 (%)
TC (blood)			-2.1859	1.6901	0.1959	-5.4884	1.1266	
		CTS	0.1219	1.7093	0.9431	-3.2282	3.4720	
		WSC	-0.5761	1.7444	0.7412	-3.9952	2.8429	
	Type	RS	-0.1338	2.0610	0.9482	-4.1733	3.9056	0.00
		CTS+RS	-6.8139	2.9481	0.0208*	-12.5920	-1.0358	
		WSC+RS	0.7024	2.3290	0.7630	-3.8624	5.2671	
		CSR	0.2677	2.3758	0.9103	-4.3889	4.9242	
			-2.7155	0.4412	< 0.0001***	-3.5802	-1.8509	0.00
	Administration period		0.0701	0.0561	1.2503	-0.0398	0.1800	
TG (blood)			1.1106	1.7676	0.5298	-2.3538	4.5750	
		CTS	-2.1980	1.7917	0.2199	-5.7097	1.3136	
		WSC	-3.0136	1.8238	0.0985	-6.5881	0.5610	
	Type	RS	-2.3077	2.1766	0.2890	-6.5738	1.9584	0.00
		CTS+RS	-4.5172	2.5911	0.0813	-9.5957	0.5613	
		WSC+RS	-2.5444	2.5135	0.3114	-7.4708	2.3821	
		CTS+VitC	-1.9712	2.5027	0.4309	-6.8764	2.9340	
			-2.0619	0.4644	< 0.0001***	-2.9721	-1.1516	5.07
	Administration period		0.1108	0.0586	0.0586	-0.0040	0.2257	
LDL-C (blood)	Type		-1.7721	1.0902	0.1041	-3.9089	0.3647	2.77
		CTS	-1.0320	1.1352	0.1041	-3.9089	0.3647	

		WSC	-1.1110	1.1886	0.3499	-3.4407	1.2186	
		RS	1.5229	1.5190	0.3161	-1.4542	4.5000	
			-2.3459	0.7447	0.0016**	-3.8056	-0.8863	0.00
	Administration period		-0.0554	0.1258	0.6595	-0.3021	0.1912	
HDL-C (blood)			0.3816	0.3323	0.2507	-0.2696	1.0329	
	Type	WSC	-1.1785	0.7190	0.1012	-2.5877	0.2307	
		RS	-0.4951	1.3894	0.7216	-3.2183	2.2282	0.00
		CTS+RS	1.6183	1.9784	0.4134	-2.2594	5.4959	
		WSC+RS	-0.1523	1.9366	0.9373	-3.9481	3.6434	
			-1.4886	0.5323	0.0052**	-2.5319	-0.4453	3.56
	Administration period		0.2432	0.0684	0.0004***	0.1091	0.3773	
TC (liver)			-1.5873	1.9416	0.4136	-5.3927	2.2181	
	Type	WSC	0.0805	2.2402	0.9713	-4.3102	4.4713	0.00
		CTS	-2.0698	1.9835	0.2967	-5.9575	1.8179	
		CSR	-3.1597	2.9633	0.2869	-8.9676	2.6481	
			-1.9173	0.7594	0.0116	-3.4057	-0.4289	12.10
	Administration period		-0.1982	0.0944	0.0358	-0.3872	-0.0132	
	Type		-3.0600	0.4819	< 0.0001***	-4.0045	-2.1154	7.30
		WSC	-1.1192	1.1754	0.3410	-3.4229	1.1845	
			-2.7837	1.0596	0.0086**	-4.8606	-0.7068	0.00
	Administration period		-0.0620	0.1197	0.6045	-0.2967	0.1727	
TC (feces)	Type		2.6479	0.3939	< 0.0001***	1.8759	3.4200	0.00
		WSC	-0.2285	1.0908	0.8341	-2.3664	1.9094	
			1.3488	0.7729	0.0810	-0.1661	2.8637	16.16

	Administration period		0.1637	0.0958	0.0808	-0.0205	0.3552	
TG (feces)			1.2205	0.8155	0.1345	-0.3778	2.8189	21.60
	Administration period		0.1409	0.0847	0.0961	-0.2510	0.3069	
TNF-α	Type		-2.0430	0.3956	< 0.0001***	-2.8184	-1.2676	22.33
		WSC	3.0273	1.4005	0.0307*	0.2823	5.7723	
			-2.4611	1.3793	0.0744	-5.1646	0.2423	
	Administration period		0.0599	0.1285	0.6413	-0.1920	0.3117	0.00
Body weight			-3.4586	0.5526	< 0.0001***	-4.5418	-2.3755	
		WSC	2.8636	0.8524	0.0008***	1.1930	4.5342	
	Type	RS	1.1231	1.3669	0.4113	-1.5559	3.8021	19.38
		CTS+RS	-5.5412	2.5456	0.0295*	-10.5305	-0.5519	
		WSC+RS	1.9751	1.7926	0.2705	-1.5383	5.4885	
			-0.5489	1.3274	0.6793	-3.1506	2.0529	
	Administration period		-0.2678	0.1770	0.1303	-0.6148	0.0792	0.00
Glucose (blood)			-0.9044	0.3993	0.0235*	-1.6869	-0.1218	
	Type	RS	-0.7644	1.3438	0.5694	-3.3982	1.8694	0.00
		CTS+RS	-0.8650	1.3491	0.5214	-3.5092	1.7793	
		CTS+VitC	1.6188	1.3082	0.2159	-0.9453	4.1829	
			-1.0118	0.8754	0.2477	-2.7275	0.7039	
	Administration period		0.0103	0.0736	0.8887	-0.1339	0.1545	0.00

40 [1] CTS, chitosan; WSC, water-soluble chitosan; RS, resistant starch; CTS+RS, chitosan and resistant starch; WSC+RS, water-soluble chitosan

41 and resistant starch; CTS+VitC, chitosan and vitamin C; CSR, cholestyramine

42 [2] Means marked with *, **, and *** differ significantly ($p<0.05$, 0.01 and 0.001, respectively)

43

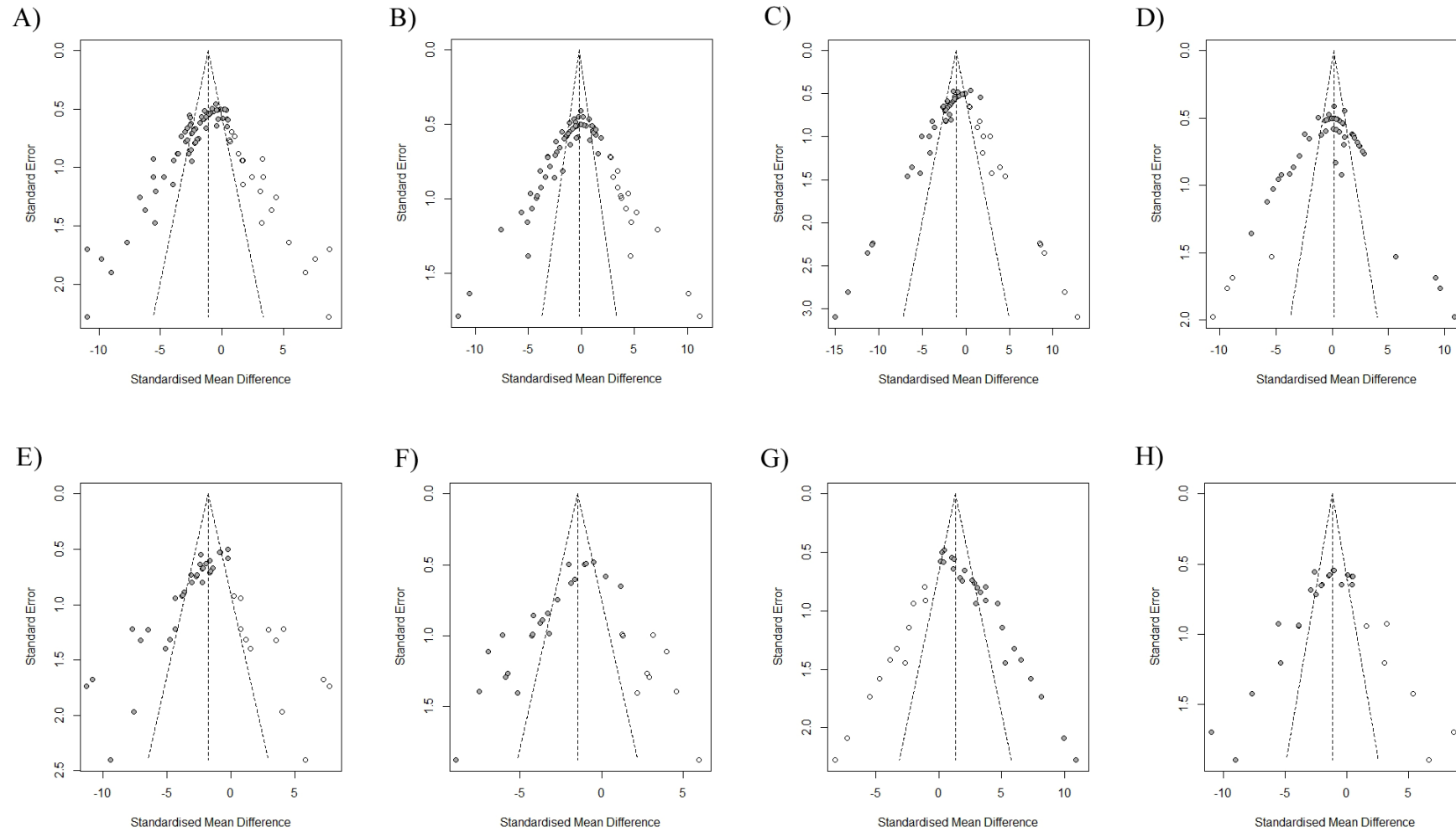44   Table 6. Egger's linear regression test for publication bias

Items	Bias	Se[1]. bias	Slope	t	df[2]	*p*-value
Total cholesterol (blood)	-6.9521793	0.5168551	2.8826324	-13.451	64	< 2.2e-16
Triglyceride (blood)	-7.4780606	0.9998057	3.7716108	-7.4795	67	2.087e-10
LDL-cholesterol (blood)	-6.1250126	0.4715822	2.2442145	-12.988	46	< 2.2e-16
HDL-cholesterol (blood)	0.51543585	1.43323094	-0.07605097	0.35963	52	< 0.0001
Total cholesterol (liver)	-6.5468325	0.5461543	2.4287577	-11.987	30	5.732e-13
Triglyceride (liver)	-6.7370699	0.9014982	2.5785977	-7.4732	21	2.411e-07
Total cholesterol (feces)	6.5339622	0.4235035	-2.6905774	15.428	24	5.871e-14
Triglyceride (feces)	8.411555	1.070048	-3.8220945	7.8609	8	4.953e-05
TNF-α (blood)	-8.347186	2.266406	3.647681	-3.683	11	0.003607
Body weight	-7.798456	1.192187	3.513530	-6.5413	20	2.249e-06

45   [1]Se: standard error

46   [2]df: degrees of freedom of Q statistic

47

48   Table 7. Trimmed effect size of probiotics on inflammatory bowel disease in murine model
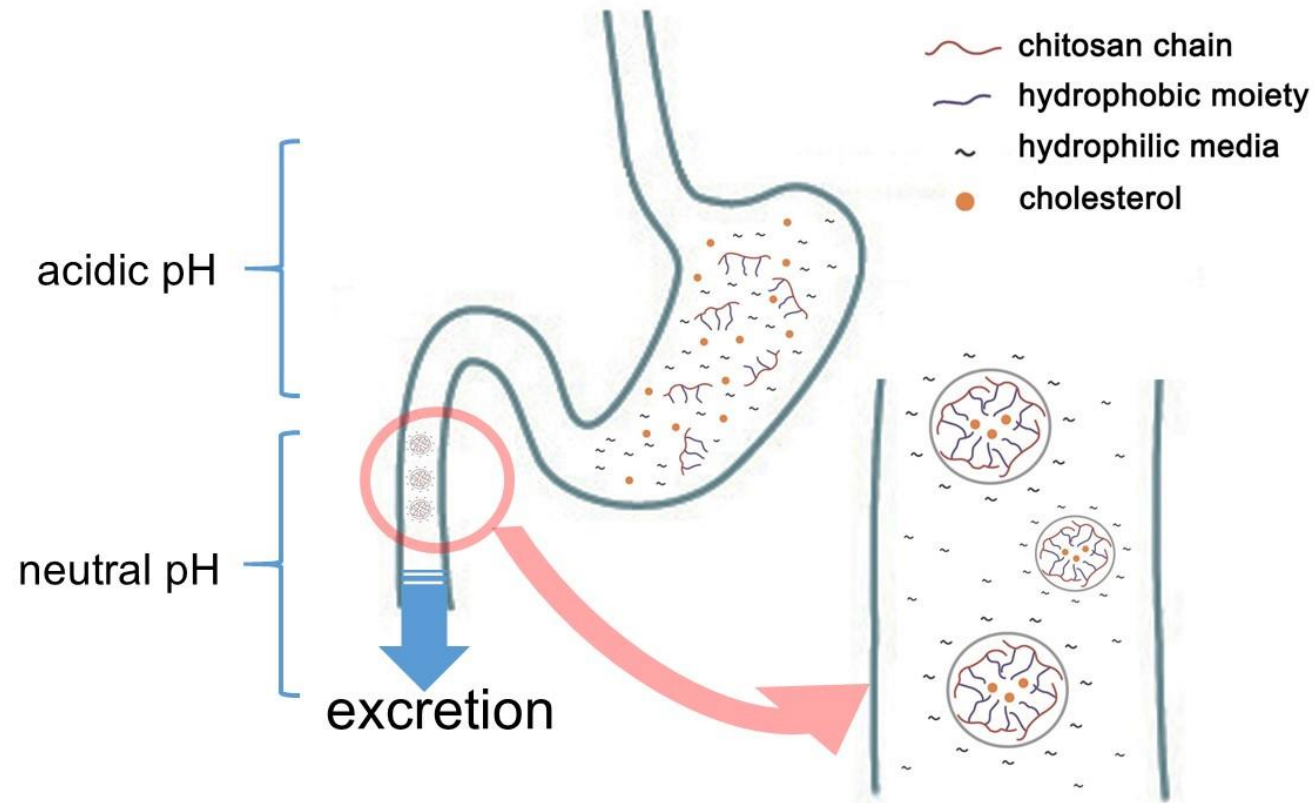
Items	df	Fixed effect model		Random effect model		Heterogeneity		
		ES	*p*-value	ES	*p*-value	Q (*p*-value)	I^2 (%)	τ^2
Total cholesterol (blood)	86	-1.1096	< 0.0001	-1.2079	< 0.0001	686.36 (< 0.0001)	87.5	3.6291
Triglyceride (blood)	78	-0.2142	0.0029	-0.2935	0.2360	878.84 (< 0.0001)	91.1	4.2254
LDL-cholesterol (blood)	64	-1.1291	< 0.0001	-1.2373	< 0.0001	551.97 (< 0.0001)	88.4	4.2350
HDL-cholesterol (blood)	52	0.0607	0.4912	-0.1870	0.5174	521.81 (< 0.0001)	90.0	3.7407
Total cholesterol (liver)	42	-1.7190	< 0.0001	-1.8509	< 0.0001	367.01 (< 0.0001)	88.6	5.8208
Triglyceride (liver)	31	-1.4703	< 0.0001	-1.6805	0.0004	314.64 (< 0.0001)	90.1	6.2275
Total cholesterol (feces)	31	1.2437	< 0.0001	1.3796	0.0004	226.78 (< 0.0001)	86.3	3.9640
Triglyceride (feces)	13	1.4815	< 0.0001	1.5692	0.0011	71.66 (< 0.0001)	81.9	2.5666
TNF-α (blood)	14	-1.2869	< 0.0001	-1.3743	0.0026	96.71 (< 0.0001)	85.5	2.5645
Body weight	27	-1.1740	< 0.0001	-1.2547	0.0079	284.88 (< 0.0001)	90.5	5.3068
Glucose (blood)	12	-0.7512	< 0.0001	-0.8958	0.0096	61.64 (< 0.0001)	80.5	1.2356

49

Figure 1.

51

52   **Figure 2.**