Asian Journal of Health Research
Journal Homepage: https://a-jhr.com
Published by Ikatan Dokter Indonesia Wilayah Jawa Timur

OPEN ACCESS

Systematic Review and Meta-Analysis

Antioxidant Supplementation Improves Lipid Profiles and Antioxidant Levels in Post-menopausal Women: Systematic Review and Meta-Analysis

Felicia Tandiono, Dyang Wulan Apriliani*, Fadhila Permata Safitri, Timothy Sahala Gerardo, Audrey Gracielle Tarigan

Faculty of Medicine, Universitas Brawijaya/dr. Saiful Anwar Hospital, Malang, East Java, Indonesia

ARTICLE HISTORY
Received: 1 November 2024
Revised: 19 January 2025
Accepted: 7 March 2025

CORRESPONDING AUTHOR*
Dyang Wulan Apriliani
dyangwln@student.ub.ac.id
Faculty of Medicine, Universitas Brawijaya/
dr. Saiful Anwar Hospital, Malang, East Java,
Indonesia

KEYWORDS
Antioxidant Supplementation; Post-menopausal; Lipid Profile; Improvement

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

ABSTRACT

Introduction: Post-menopause is marked by a decline in estrogen levels around age 50, leading to unfavorable metabolic changes, including increased LDL-c and decreased HDL-c, which elevate cardiovascular disease (CVD) risk. Reduced antioxidant capacity during this phase also heightens oxidative stress, contributing to chronic diseases such as CVD, osteoporosis, and cancer. Given the limitations of conventional treatments, antioxidant supplementation has emerged as a potential alternative.

Material and Methods: Systematic Reviews and Meta-Analyses Preferred Reporting Items (PRISMA) framework was used in this study. Studies on arterial ligation techniques in placenta percreta surgery were included based on criteria focusing on estimated blood loss, operative time, and adverse events. A comprehensive literature search across multiple databases was performed, resulting in three studies that met the inclusion criteria.

Results: The three studies included in the review with a total of 193 patients. The findings show that IIAL significantly decreased the projected amount of blood loss compared to control groups. In one study, bilateral IIAL showed lower blood loss (1076 ± 545 ml) compared to other interventions, while another study demonstrated that IIAL resulted in lower estimated blood loss compared to control groups. However, hypogastric artery ligation (HAL) was associated with higher blood loss in one study. Despite its effectiveness in controlling blood loss, complications such as common iliac artery thrombosis, pseudoaneurysms, and limb ischemia were reported, though with low incidence.

Conclusion: Arterial ligation, particularly IIAL, could be a viable strategy for managing blood loss during placenta percreta surgery.

Cite this as: Tandiono F, Apriliani DW, Safitri FP, Gerardo TS, Tarigan AG (2025) Antioxidant Supplementation Improves Lipid Profiles and Antioxidant Levels in Post-menopausal Women: Systematic Review and Meta-Analysis. *Asian J Heal Res*. 4 (1): 88–100. doi: 10.55561/ajhr.v4i1.179

INTRODUCTION

Post-menopause, defined as the cessation of menstrual cycles typically around the age of 50, involves significant hormonal changes, primarily the decline in estrogen levels [1,2]. This hormonal shift is associated with metabolic alterations, including an unfavorable lipid profile characterized by elevated LDL cholesterol and reduced HDL cholesterol levels, increasing cardiovascular disease risk [3]. Studies have shown that approximately 70% of women aged 60 and older have one or more risk factors for heart disease, and the risk of CVD rises significantly post-menopause due to changes in lipid profiles and hormonal shifts. Additionally, post-menopausal women often experience a decrease in antioxidant capacity, leading to heightened oxidative stress—a critical factor in the development of various chronic conditions such as cardiovascular diseases, osteoporosis, and potentially cancer [4]. The general effects of menopause on lipid metabolism and antioxidant status underscore the heightened susceptibility to chronic diseases during this life stage.

Traditional treatments for menopause, including hormone replacement therapy (HRT) and non-hormonal medications, present notable limitations [5,6]. HRT, comprising estrogen and progesterone, is associated with increased risks of breast cancer, heart disease, stroke, and thromboembolism, prompting concerns over its long-term safety. Both hormonal and non-hormonal therapies can also elicit adverse effects like bloating, breast tenderness, mood swings, and sexual dysfunction, influencing treatment adherence and overall well-being. Furthermore, accessibility and cost considerations pose barriers to treatment initiation and continuity, potentially restricting healthcare options for specific demographics [6]. Integrating antioxidant supplementation into menopausal management presents a promising opportunity to address these challenges.

Antioxidants are bioactive compounds crucial in mitigating oxidative stress by scavenging free radicals, unstable molecules implicated in cellular damage, and aging processes [7,8]. Their primary function is neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby preserving cellular integrity and reducing the risk of oxidative damage to biomolecules like lipids, proteins, and DNA. Previous research underscores the profound health implications of antioxidants, with studies indicating a notable reduction in chronic disease risk associated with higher antioxidant intake. For instance, a meta-analysis demonstrated a significant 62% decrease in cardiovascular disease risk among individuals consuming diets rich in antioxidants [9]. Several supplements showing antioxidant potencies include vitamins C and E, seeds, vegetable oils, beta-carotene-rich foods, flavonoids, isoflavones (found in soybeans and legumes), selenium, and zinc [9–11].

There is still a lack of systematic reviews and meta-analyses that comprehensively evaluate the effectiveness of antioxidant supplementation in improving lipid profile and antioxidant capacity among post-menopausal women, particularly with randomized controlled trials (RCTs) design. Due to this research gap, we have utilized recent relevant RCTs to conduct this systematic review, aiming to explore the potential benefits of antioxidants in enhancing lipid profile and antioxidant capacity in post-menopausal women.

MATERIAL AND METHODS

This review was based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [12].

Eligibility Criteria

Inclusion and exclusion criteria were decided upon before the literature search to improve the review's specificity. Randomized controlled studies published within the past ten years met the inclusion criteria. Stages of menopause included only menopause and post-menopausal women as the sample population. As part of the intervention, the patients received antioxidant supplements in various forms, including isoflavone-enriched foods (Cornu mas extract, soy protein powder, dried plums), avenanthramide, Korean red ginseng, green tea extract, genistein, and Vitamin E.

The PICOS framework is used for inclusion criteria consisting of 1) Population: post-menopausal women; 2) Intervention: Antioxidant supplementation (isoflavone enriched foods, zinc, vitamin C or E, and plant extract); 3) Comparison: patients treated with conventional therapy or placebo group; 4) Outcome: Lipid profile (TG-c, LDL-c, HDL-c, and Total-c) and antioxidant capacity (SOD, GPX, and TAC); 5) Study design: Randomized Controlled Trial (RCT). Exclusion criteria were adopted: 1) irrelevant to the study's aim; 2) non-human trials and studies; 3) non-English studies and grey literature; 4) protocol studies.

Search Strategy

From Mei 12 to June 8, 2024, three independent researchers (DWA, FT, and FPS) searched the literature. Numerous databases were utilized, such as ScienceDirect, PubMed, EbscoHost, ProQuest, SpringerLink, and the Cochrane Journal. The keywords used (("Post-menopause" OR "menopause") AND ("antioxidant" OR "dietary supplementation" OR "Vitamin C" OR "Vitamin E") AND ("lipid profile" OR "antioxidant capacity" OR "serum marker)").

Data Extraction and Analysis

Three authors (TSG, AGT, and FT) separately extracted the chosen studies into a Google Sheet, and then all authors evaluated the studies' correctness and eligibility. The other authors overseeing the process, FPS, examined and documented them. Discussions were used to settle disagreements that arose during the writing process.

Risk of Bias Assessment

Cochrane Risk of Bias Tool 2 for Randomized Controlled Trials was used by FT to assess the risk of bias in the chosen studies. The other writers oversaw the procedure. The instrument has five domains: randomization, deviances from the intended interventions, incomplete outcome data, outcome measurement, and reported result selection. The domains were split into three categories based on the study's quality: low, moderate, and high risk of bias [18].

The meta-analysis was conducted using Review Manager 5.4, and the data was assessed based on the mean change from the baseline data. The data was classified as continuous with a 95% confidence interval

(CI). Additionally, the outcome analysis was conducted using the random effect model with a standardized mean difference, as the statistical procedure was the inverse variance model, and the heterogeneity and differences in the length of the studies were. The *p-value* < 0.05 is considered significant.

Intervention of Interest

According to recent research, antioxidant supplementation shows promise in improving lipid profiles and antioxidant levels in post-menopausal women [13–15]. It could benefit women because it helps eliminate oxidative stress within the body, promotes bone health and cognitive function, and reduce the risk of cardiovascular and cancer diseases. In the past decade, researchers have increasingly focused on exploring the connection between antioxidants and improving lipid profiles and antioxidant capacity in post-menopausal women. Therefore, this review explores the potential of antioxidant supplementation in improving lipid profiles and antioxidant capacity in post-menopausal symptoms.

Outcome of Interest

The mean changes in lipid (TG-c, LDL-c, HDL-c, Total-c) and antioxidant markers (GPX, SOD, TAC) from pre-intervention to post-intervention in each of the included studies were the focus of this review. Multiple outcomes were assessed to enhance the comprehensiveness of this review and thoroughly elucidate the efficacy of antioxidants as an alternative therapy for post-menopausal women.

RESULTS

Study Selection and Identification

A comprehensive literature search identified 2351 articles published within the last decade across six databases. Of these, 1355 duplicates were removed. An additional 699 articles were excluded due to ineligibility, including review articles, books, protocol studies, and inaccessible articles due to subscription constraints. Furthermore, 264 articles did not meet the predefined inclusion criteria for study design. As depicted in Figure 1 of the PRISMA flowchart, these exclusions led to the inclusion of 13 articles in the systematic review for quantitative analysis (Fig.1).

Risk of Bias Assessment

Based on the risk of bias evaluation, only two studies were assessed to have an unclear risk due to insufficiently detailed methodological descriptions in the first, second, and fifth domains of the Cochrane Risk of Bias Tool 2. The remaining studies (n=11) were considered to have a low risk of bias (Fig.2). Despite varying levels of bias across the included studies, comprehensive data were adequate for the study's analysis.

Summaries of the Included Studies

This review encompassed thirteen randomized controlled trials investigating various forms and doses of antioxidant interventions. These interventions included isoflavones, zinc, vitamins C and E, and extracts such as Cornu mas, soy protein powder, dried plums, avenanthramides from oats, Korean red ginseng, green tea extract, genistein, and vitamin E. These compounds are recognized for combating oxidative stress by neutralizing free radicals. A total of 934 post-menopausal women, ranging in age from 52 to 66 years, participated in the studies. The intervention durations spanned from 4 weeks to 6 months. The studies analyzed changes in lipid profiles, including triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and total cholesterol (Total-c), comparing pre- and post-intervention values. Additionally, improvements in antioxidant capacity were assessed using three markers: superoxide dismutase (SOD), glutathione peroxidase (GPX), and total antioxidant capacity (TAC). Table 1 presents an overview of the included studies.

Meta-analysis of Antioxidant Potencies in Improving Antioxidant Capacity

In this subgroup analysis, seven studies compared the total antioxidant levels improvement in post-menopausal women between the antioxidant group and the placebo. Despite the presence of three antioxidant markers (SOD, TAC, GPX) in the study, these markers were collectively analyzed in a single analytical group due to their shared representation of antioxidant levels. To mitigate potential biases stemming from differences among the markers analyzed, the authors employed Standard Mean Differences (SMD) analysis. Antioxidants significantly increased the total antioxidant capacity 1.61 times higher than the placebo group (SMD: 1.61, 95%CI: 0.84 to 2.37, p=0.0001), respectively. Based on the analysis, antioxidants were superior and could improve antioxidant markers better than placebo (Fig.3).

Meta-analysis of Antioxidant Potencies in Improving Lipid Profile

In this subgroup analysis involving eight studies of post-menopausal women, researchers assessed the differences in total cholesterol levels between those receiving antioxidant supplements and those given placebos. The findings revealed a statistically significant decrease in total cholesterol among those in the

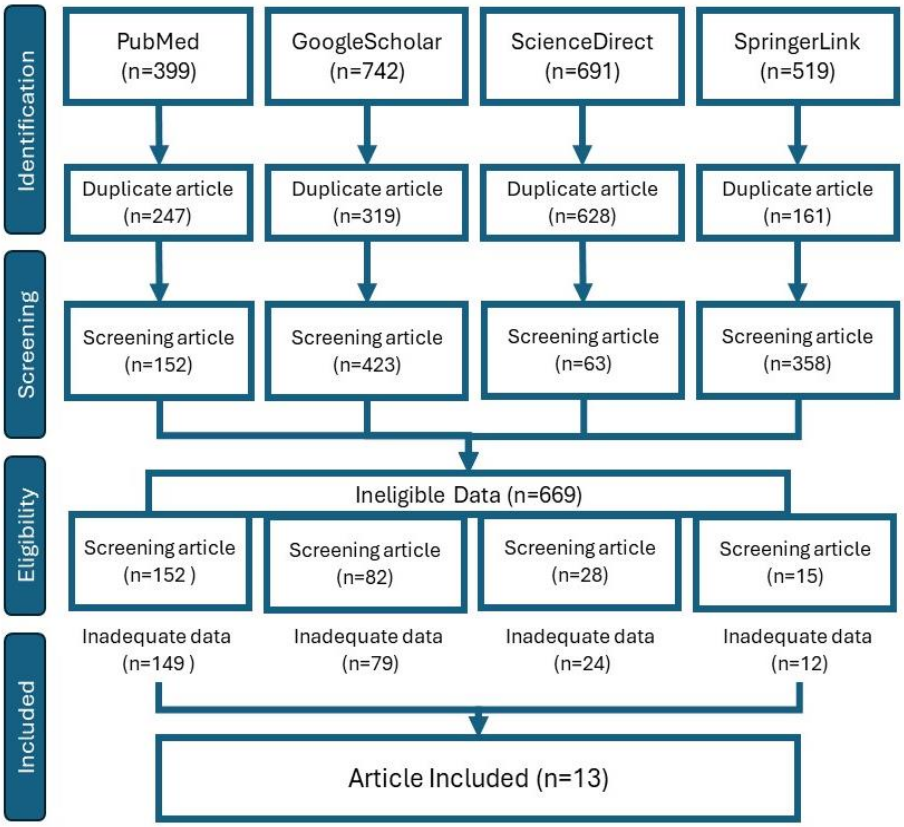


Fig.1. PRISMA Flowchart

antioxidant group compared to the placebo group (MD: -11.63, 95% CI: -16.56 to -6.71, $p < 0.0001$). Suggests that antioxidant supplementation led to an average reduction of 11.63 units in total cholesterol levels, highlighting the positive impact of antioxidants on lipid profiles compared to placebos (Fig.4).

Furthermore, in the subgroup analysis, the mean differences in LDL cholesterol (LDL-c) levels between post-menopausal women receiving antioxidant supplements and those receiving placebos demonstrated a significant reduction in LDL-c levels in the antioxidant group compared to the placebo group (MD: -6.19, 95% CI: -8.62 to -3.77, $p < 0.0001$). Suggests that antioxidant supplementation led to an average decrease of 6.19 units in LDL cholesterol levels. These findings emphasize the potential effectiveness of antioxidants in improving LDL-c profiles compared to placebo interventions (Fig.5).

Similar to evaluating LDL cholesterol (LDL-c) levels, researchers examined the mean differences in triglyceride (TG-c) levels between individuals receiving antioxidant supplements and those receiving placebos. The results showed a significant decrease in TG-c levels in the antioxidant group compared to the placebo group (MD: -10.27, 95% CI: -14.98 to -5.56, $p < 0.0001$), indicating an average reduction of 10.27 units in triglyceride levels due to antioxidant supplementation. These findings highlight the potential of antioxidants to improve triglyceride profiles compared to placebo treatments effectively (Fig.6).

Meanwhile, the subgroup analysis assessed the mean differences in high-density lipoprotein cholesterol (HDL-c) levels between participants receiving antioxidant supplements and those receiving placebos, indicating a significant increase in HDL-c levels in the antioxidant group compared to the placebo group (MD: 2.82, 95% CI: 1.61 to 4.03, $p < 0.0001$), demonstrating an average increase of 2.82 units in HDL cholesterol due to antioxidant supplementation (Fig.7).

DISCUSSION

This study involved a systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials to assess the impact of antioxidant consumption on the lipid profile and antioxidant capacity of post-menopausal women. We found that taking antioxidants in various forms for 4 up to 24 weeks

increased total antioxidant capacity and HDL-c levels, followed by significantly decreased LDL-c, TG-c, and Total-c levels more than the placebo group. Our findings are consistent with previous studies on the effectiveness of antioxidant supplementation. In managing high lipid profiles in post-menopausal women, hormone replacement therapy is not typically first-line; instead, dietary and lifestyle changes are recommended according to the US National Cholesterol Education Program Adult Treatment Panel III guidelines. Recent research highlights the effectiveness of dietary supplements in this context [6].

Post-menopausal women are encouraged to enhance their intake of exogenous antioxidants, such as vitamins (like vitamin A, β-carotene, vitamin C, and vitamin E), plant flavonoids, and soy isoflavones. These beneficial nutrients are commonly found in various foods, including fruits, vegetables, soybeans, cocoa, and tea leaf extracts. Prosperous sources of antioxidants include almonds, artichokes, blackberries, blueberries, sour cherries, chokeberries, dark unsweetened chocolate, cloves, ground cranberry juice, coffee, cranberries, grape juice, pomegranate juice, pecans, raspberries, spinach, strawberries, walnuts, and red wine [3,16,17].

Antioxidants are characterized by molecular structures featuring multiple bonds and aromatic rings, enabling them to act effectively as reducing agents. By trapping free radicals and preventing processes like lipid peroxidation, they play a critical role in stopping oxidative chain reactions. Depending on their quantity, the highly reactive byproducts of lipid peroxidation can have a major impact on proteins, DNA, and cell signaling [5,6,11]. Thus, incorporating antioxidants into the diet through oral supplementation offers a promising strategy to mitigate oxidative stress-related diseases in post-menopausal women.

A study by Bourgonje et al. (2020) examined serum-free thiols (R-SH) in Omani women, finding significantly lower levels in post-menopausal compared to premenopausal participants (762.9 ± 85.3 vs. 780 ± 80.9 μM, age-adjusted $p < 0.001$) [5]. Another investigation focused on antioxidant vitamins C and E in post-menopausal women. It highlighted their role in maintaining a favorable oxidative balance by reducing malonaldehyde levels and enhancing antioxidant enzyme activity, potentially lowering cardiovascular disease risk by inhibiting cholesterol synthesis and LDL-cholesterol oxidation [18,19]. A study by Tadayon et al. (2018) involving 79 women demonstrated that green tea significantly reduced total cholesterol (mean difference −18.1 vs. −5 mg/dL compared to placebo, $p < 0.04$), triglycerides, and LDL cholesterol [20]. Furthermore, a meta-analysis by Siyan et al. indicated that soy protein with isoflavones lowered total cholesterol by 0.22 mmol/L (3.77%), LDL cholesterol by 0.21 mmol/L (5.25%), and triglycerides by 0.10 mmol/L (7.27%) while increasing HDL cholesterol by 0.04 mmol/L (3.03%) [21]. Additionally, research by Gholamrezayi et al. (2019) on Cornelian cherry extract demonstrated reductions in weight, BMI, waist circumference, LDL to HDL ratio, and total cholesterol to HDL ratio, alongside increases in HDL and ApoA1 levels. Following Cornelian cherry extract supplementation, significant improvements were noted in fasting insulin and insulin resistance index [22].

Oxidative stress, a hallmark of aging, arises from an excessive production of reactive oxygen species (ROS) that overwhelm the body's antioxidant defenses. Typically, antioxidants neutralize ROS to prevent cellular damage. However, with aging, antioxidant levels decline, leaving cells vulnerable to oxidative damage. This process is implicated in the pathogenesis of age-related diseases such as non-alcoholic liver cirrhosis and atherosclerotic heart disease [13,18]. Compared to premenopausal women, postmenopausal women frequently show higher levels of oxidative stress, as shown by pro-oxidant biomarkers such as glutathione, 4-hydroxynenal, and malondialdehyde, as well as inflammatory cytokines.

These markers indicate increased oxidative damage and stress during the post-menopausal phase. Studies have linked oxidative stress in post-menopausal women to disturbances in lipid metabolism. Oxidative stress can directly affect lipid metabolism by oxidizing lipids, particularly low-density lipoproteins (LDL), which can lead to oxidized LDL (ox-LDL) formation. Ox-LDL promotes atherosclerosis by triggering inflammation and contributing to plaque development in arterial walls. Furthermore, oxidative stress can alter lipid metabolism indirectly through its effects on insulin sensitivity and adipocyte function. Increased oxidative stress may impair insulin signaling pathways, leading to insulin resistance, perturbing lipid metabolism, and promoting dyslipidemia. Dyslipidemia, characterized by elevated levels of LDL cholesterol and triglycerides, is a significant risk factor for cardiovascular diseases [23].

Several biases have been identified in this study, mainly stemming from small sample sizes and variability in the types and dosages of antioxidants. These factors contribute to clinical heterogeneity, introducing variability in therapeutic regimens such as dosage levels, preparation methods, administration schedules, and measured outcomes. Researchers are mindful of these limitations, which can misinterpret the generalizability of study findings. To advance understanding in this area, further research is needed. Specifically, investigations are required to determine the optimal dosage and duration of antioxidant supplementation and establish comprehensive safety profiles. Additionally, identifying the most effective types of antioxidants for addressing the needs of post-menopausal women remains a priority. It involves assessing efficacy and considering factors

such as antioxidant bioavailability and pharmacokinetics, which influence how these compounds are absorbed, distributed, metabolized, and eliminated within the body.

CONCLUSION

The subgroup analyses involving post-menopausal women demonstrate significant benefits of antioxidant supplementation compared to placebos across several markers. Antioxidant supplements markedly increased total antioxidant capacity, indicating superior improvement in antioxidant levels. Moreover, antioxidant supplementation substantially reduced total cholesterol, LDL cholesterol, and triglyceride levels while significantly increasing HDL cholesterol. These findings highlight the potential of antioxidants to enhance cardiovascular health profiles in menopausal women, suggesting a beneficial role in mitigating lipid-related risks associated with this population. Further research should focus on refining antioxidant intervention protocols to optimize their clinical application and better understand their comprehensive health benefits in menopausal women.

ACKNOWLEDGMENT

We thank all contributors for their work in creating the paper. We would also like to express our gratitude to Dr.dr. Sutrisno, Sp.OG.Subsp.FER for the supervision during the conceptualization and writing of this paper.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

REFERENCES

1. Aninye IO, Laitner MH, Chinnappan S. Menopause preparedness: Perspectives for patient, provider, and policymaker consideration. Menopause. 2021;28(10):1186–91.
2. Menopause : diagnosis and management. 2019;(December).
3. Giacobbe A, Bitto A, Arcoraci V, Granese R, D'Anna R. A New Supplement for the Treatment of Metabolic Syndrome in Postmenopausal Women. Food Nutr Sci. 2020;11(01):23–31.
4. Farshbaf-Khalili A, Ostadrahimi A, Mirghafourvand M, Ataei-Almanghadim K, Dousti S, Iranshahi AM. Clinical Efficacy of Curcumin and Vitamin e on Inflammatory-Oxidative Stress Biomarkers and Primary Symptoms of Menopause in Healthy Postmenopausal Women: A Triple-Blind Randomized Controlled Trial. J Nutr Metab. 2022;2022.
5. Bourgonje AR, Abdulle AE, Al-Rawas AM, Al-Maqbali M, Al-Saleh M, Enriquez MB, et al. Systemic oxidative stress is increased in postmenopausal women and independently associates with homocysteine levels. Int J Mol Sci. 2020;21(1).
6. Doshi S, Agarwal A. The role of oxidative stress in menopause. J Midlife Health. 2013;4(3):140.
7. Liu ZM, Ho SC, Chen YM, Xie YJ, Huang ZG, Ling WH. Research protocol: Effect of natural S-equol on blood pressure and vascular function- a six-month randomized controlled trial among equol non-producers of postmenopausal women with prehypertension or untreated stage 1 hypertension. BMC Complement Altern Med [Internet]. 2016;16(1):1–9. Available from: http://dx.doi.org/10.1186/s12906-016-1065-5
8. Yang S, Zeng Q, Huang X, Liang Z, Hu H. Effect of Isoflavones on Blood Lipid Alterations in Postmenopausal Females: A Systematic Review and Meta-Analysis of Randomized Trials. Adv Nutr [Internet]. 2023;14(6):1633–43. Available from: https://doi.org/10.1016/j.advnut.2023.09.008
9. Parohan M, Anjom-Shoae J, Nasiri M, Khodadost M, Khatibi SR, Sadeghi O. Dietary total antioxidant capacity and mortality from all causes, cardiovascular disease and cancer: a systematic review and dose–response meta-analysis of prospective cohort studies. Eur J Nutr [Internet]. 2019;58(6):2175–89. Available from: http://dx.doi.org/10.1007/s00394-019-01922-9
10. Braxas H, Rafraf M, Karimi Hasanabad S, Asghari Jafarabadi M. Effectiveness of Genistein Supplementation on Metabolic Factors and Antioxidant Status in Postmenopausal Women With Type 2 Diabetes Mellitus. Can J Diabetes [Internet]. 2019;43(7):490–7. Available from: https://doi.org/10.1016/j.jcjd.2019.04.007
11. Takahashi M, Miyashita M, Suzuki K, Bae SR, Kim HK, Wakisaka T, et al. Acute ingestion of catechin-rich green tea improves postprandial glucose status and increases serum thioredoxin concentrations in postmenopausal women. Br J Nutr. 2014;112(9):1542–50.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Rev Panam Salud Publica/Pan Am J Public Heal. 2022;46:1–11.
13. Radkhah N, Zarezadeh M, Jamilian P, Ostadrahimi A. The Effect of Vitamin D Supplementation on Lipid Profiles: an Umbrella Review of Meta-Analyses. Adv Nutr [Internet]. 2023;14(6):1479–98. Available from:

https://doi.org/10.1016/j.advnut.2023.08.012
14. Wolters M, Dejanovic GM, Asllanaj E, Günther K, Pohlabeln H, Bramer WM, et al. Effects of phytoestrogen supplementation on intermediate cardiovascular disease risk factors among postmenopausal women: A meta-analysis of randomized controlled trials. Menopause. 2020;27(9):1081–92.
15. Kanadys W, Baranska A, Jedrych M, Religioni U, Janiszewska M. Effects of red clover (Trifolium pratense) isoflavones on the lipid profile of perimenopausal and postmenopausal women—A systematic review and meta-analysis. Maturitas. 2020;132(March 2019):7–16.
16. Rezasoltani P, Elliyoun N, Ziaie T, Sobhani A, Leyli EK, Aski SK. Double-blind controlled trial of vitamin e effects on serum lipid profile in menopausal women. Diabetes, Metab Syndr Obes. 2021;14:1053–60.
17. Tuhumury HCD. EFFECT OF SOY ISOFLAVONES ON THE SERUM LIPID PROFILE AND VASCULAR FUNCTION Soybeans are unique among the legumes because they are a concentrated source of isoflavones . A number of components of soy have been studied to investigate their potential effect. J Teknol Pertan. 2015;4(1).
18. Sathyapalan T, Aye M, Rigby AS, Thatcher NJ, Dargham SR, Kilpatrick ES, et al. Soy isoflavones improve cardiovascular disease risk markers in women during the early menopause. Nutr Metab Cardiovasc Dis [Internet]. 2018;28(7):691–7. Available from: https://doi.org/10.1016/j.numecd.2018.03.007
19. Giolo JS, Costa JG, da Cunha-Junior JP, Pajuaba ACAM, Taketomi EA, de Souza A V., et al. The effects of isoflavone supplementation plus combined exercise on lipid levels, and inflammatory and oxidative stress markers in postmenopausal women. Nutrients. 2018;10(4):1–11.
20. Tadayon M, Movahedi S, Abedi P, Syahpoosh A. Impact of green tea extract on serum lipid of postmenopausal women: A randomized controlled trial. J Tradit Complement Med [Internet]. 2018;8(3):391–5. Available from: https://doi.org/10.1016/j.jtcme.2017.07.005
21. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. Am J Clin Nutr [Internet]. 2005;81(2):397–408. Available from: https://doi.org/10.1093/ajcn.81.2.397
22. Gholamrezayi A, Aryaeian N, Rimaz S, Abolghasemi J, Fallah S, Moradi N, et al. The effect of Cornus mas fruit extract consumption on lipid profile, glycemic indices, and leptin in postmenopausal women— A randomized clinical trial. Phyther Res. 2019;33(11):2979–88.
23. Rivera-Mancía S, Jiménez-Osorio AS, Medina-Campos ON, Colín-Ramírez E, Vallejo M, Alcántara-Gaspar A, et al. Activity of antioxidant enzymes and their association with lipid profile in Mexican people without cardiovascular disease: An analysis of interactions. Int J Environ Res Public Health. 2018;15(12).
24. Koenig R, Dickman JR, Kang C, Zhang T, Chu YF, Ji LL. Avenanthramide supplementation attenuates exercise-induced inflammation in postmenopausal women. Nutr J. 2014;13(1):1–11.
25. Chung TH, Kim JH, Seol SY, Kim YJ, Lee YJ. The effects of korean red ginseng on biological aging and antioxidant capacity in postmenopausal women: A double-blind randomized controlled study. Nutrients. 2021;13(9):1–12.
26. Hong MY, Kern M, Nakamichi-Lee M, Abbaspour N, Ahouraei Far A, Hooshmand S. Dried Plum Consumption Improves Total Cholesterol and Antioxidant Capacity and Reduces Inflammation in Healthy Postmenopausal Women. J Med Food. 2021;24(11):1161–8.
27. Seo SK, Hong Y, Yun BH, Chon SJ, Jung YS, Park JH, et al. Antioxidative effects of Korean red ginseng in postmenopausal women: A double-blind randomized controlled trial. J Ethnopharmacol [Internet]. 2014;154(3):753–7. Available from: http://dx.doi.org/10.1016/j.jep.2014.04.051
28. Rondanelli M, Gasparri C, Perna S, Petrangolini G, Allegrini P, Fazia T, et al. A 60-Day Green Tea Extract Supplementation Counteracts the Dysfunction of Adipose Tissue in Overweight Post-Menopausal and Class I Obese Women. Nutrients. 2022;14(24).

No	Study (year)	Study Design	D1	D2	D3	D4	D5	Overal Risk of Bias
1	Gholamrezayi et al 2019	RCT						5/5 Low Risk of Bias
2	Koenig et al 2014	RCT						5/5 Low Risk of Bias
3	Chung et al 2021	RCT						3/5 Moderate Risk of Bias
4	Rondanelli et al 2022	RCT						5/5 Low Risk of Bias
5	Sathyapalan et al 2018	RCT						5/5 Low Risk of Bias
6	Hong et al 2021	RCT						4/5 Low Risk of Bias
7	Braxas et al 2019	RCT						5/5 Low Risk of Bias
8	Khalili et al 2016	RCT						5/5 Low Risk of Bias
9	Rezasoltani et al 2021	RCT						3/5 Moderate Risk of Bias
10	Tadayon et al 2018	RCT						5/5 Low Risk of Bias
11	Giolo et al 2018	RCT						4/5 Low Risk of Bias
12	Seo et al 2014	RCT						5/5 Low Risk of Bias
13	Giacobbe et al 2020	RCT						4/5 LowRisk of Bias

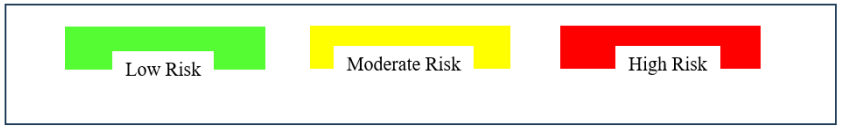


Fig.2. Cochrane Risk of Bias Tool 2 for Randomized Controlled Trial Studies

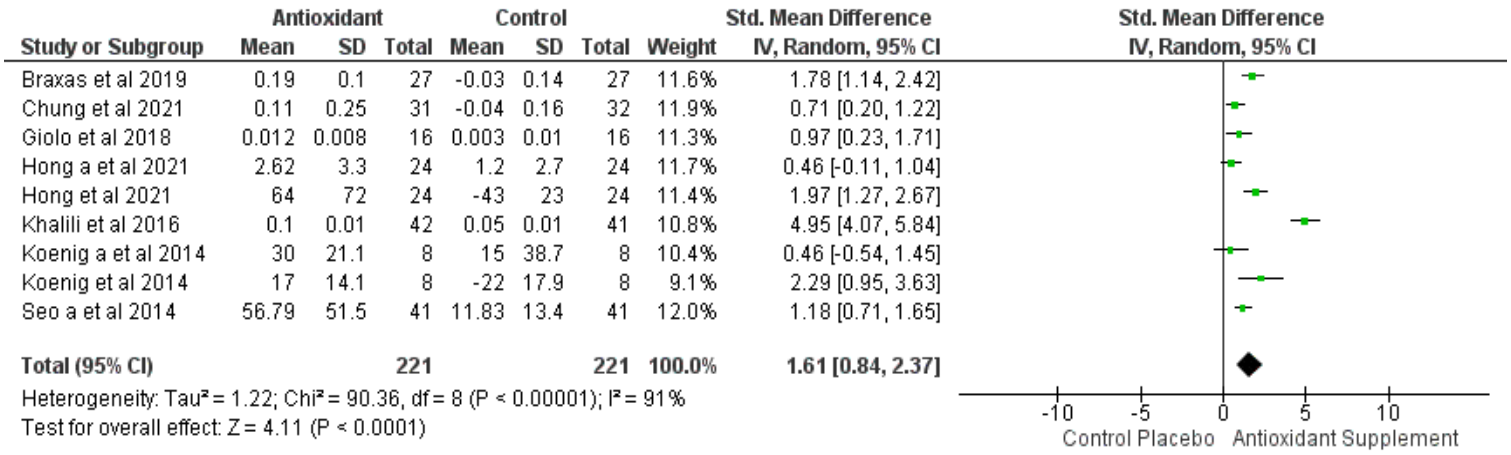


Fig.3. Standard Mean Differences of Total Antioxidant Capacity

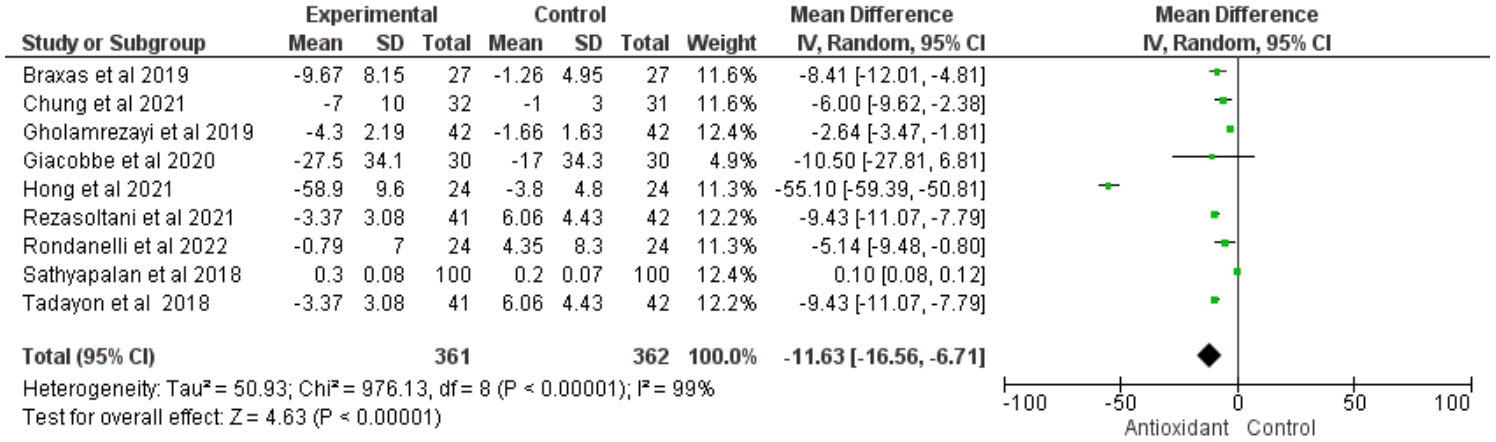


Fig.4. Mean Difference of Total Cholesterol between Antioxidant Group vs Placebo

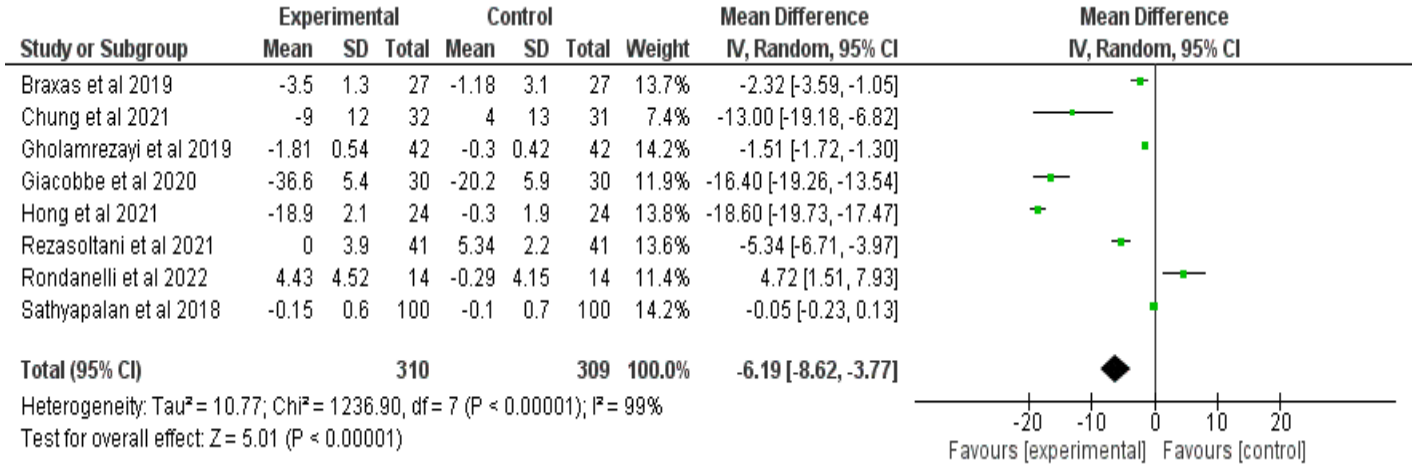


Fig.5. Mean Difference of LDL-c between Antioxidant Group vs Placebo

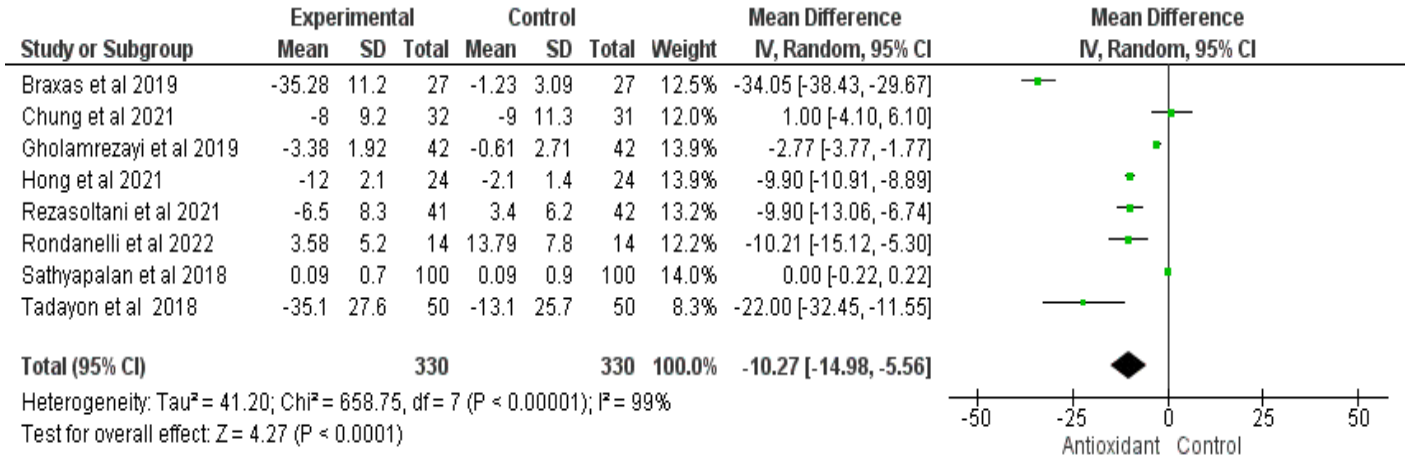


Fig.6. Mean Difference of TG-c between Antioxidant Group vs Placebo

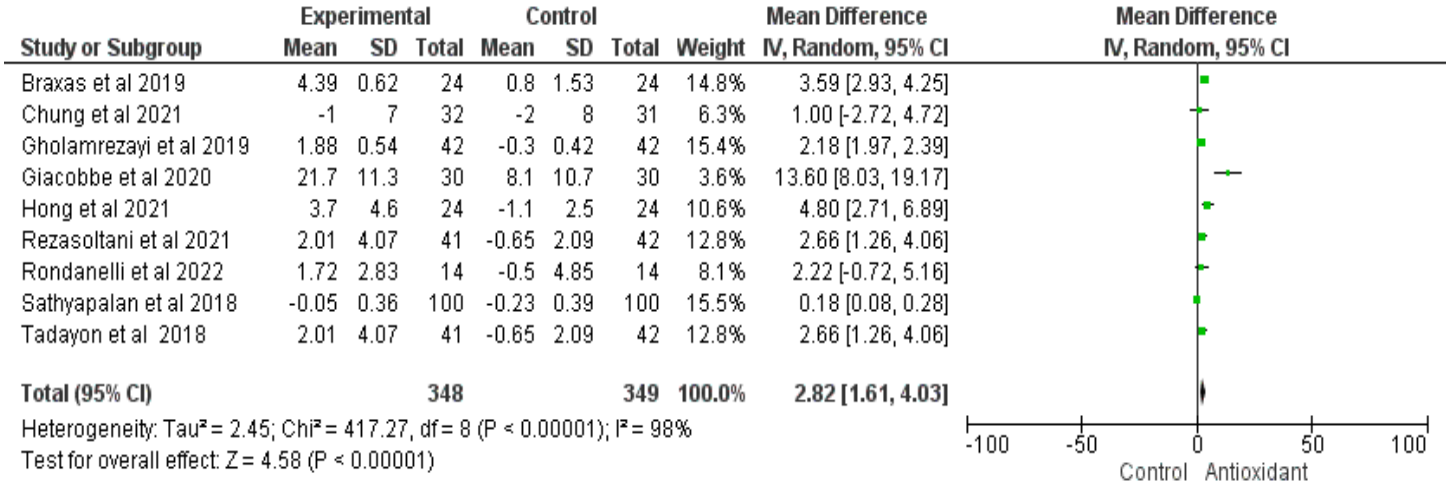


Fig.7. Mean Difference of HDL-c between Antioxidant Group vs Placebo

Table 1. Summaries included Studies

No	Study	Study Design	Sample	Type & Duration of Intervention			Antioxidant Capacity					
							TAC mmol/L		SOD U/mL		GPX nM/mL	
				Intervention	Placebo	Duration of Treatment	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)
1	Koenig et al. 2014 [24]	RCT	16	Two cookies containing 9.2 mg AVA	Two cookies containing 0.4 mg AVA	8 weeks	-	-	30 ± 21.1	15 ± 38.7	17 ± 14.1	-22 ± 17.9
2	Chung et al. 2021 [25]	RCT	63	2 g of KRG tablet per day	Placebo tablet	8 weeks	0.11 ± 0.25	−0.04 ± 0.16	-	-	-	-
3	Hong et al. 2021 [26]	RCT	48	100 g dried plums/day	0 g/day	6 months	-	-	2.62 + 3.3	1.2 + 2.7	64 + 152	-43 + 23
4	Braxas et al. 2019 [10]	RCT	54	2 genistein capsules daily for	2 placebo capsules daily	12 weeks	0.19 + 0.1	-0.03 + 0.14	-	-	-	-
5	Khalili et al. 2016 [4]	RCT	84	One 500mg capsule of vitamin E twice a day	Two placebo capsules containing 500mg daily	8 weeks	0.1 + 0.01	0.05 + 0.01	-	-	-	-
6	Giolo et al. 2018 [19]	RCT	32	exercises + 100 mg of isoflavone	Exercise + placebo	10 weeks	-	-	0.012 ± 0.008	0.003 ± 0.010	-	-
7	Seo et al. 2014 [27]	RCT	82	3 g red ginseng daily	Placebo tablet	12 weeks	-	-	56.79 + 51.56	11.83 + 48.41	-	-

Table 1. Continued

No	Study	Study Design	Sample	Type & Duration of Intervention			Lipid Profiles							
							TG-c mg/dL		LDL-c mg/dL		HDL-c mg/dL		Total-c mg/dL	
				Intervention	Placebo	Duration of Treatment	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)	Intervention (Mean Changes/SD)	Control (Mean Changes/SD)
1	Gholamrezayi et al. 2019 [22]	RCT	84	Three capsules of 300 mg of Cornus mas extract	Three capsules of 300 mg of starch powder	8 weeks	−3.38 ± 1.92	−0.61 ± 2.71	- 1.88 ± 0.54	−0.3 ± 0.42	1.88 ± 0.54	−0.3 ± 0.42	−4.3 ± 2.19	−1.66 ± 1.63
2	Chung et al. 2021 [25]	RCT	63	2 g of KRG tablet per day	Placebo tablet	8 weeks	-8 ± 9.2	−9 ± 11.3	−9 ± 12	4 ± 13	-1 ± 7	−2 ± 8	−7 ± 10	−1 ± 3
3	Rondanelli et al. 2022 [28]	RCT	28	2x daily 150 mg of Green Tea Extract	Placebo tablet	8 weeks	3.58 ± 5.2	13.79 ± 19.6	4.43 ± 4.52	-0.29 ± 4.15	1.72 ± 2.83	- 0.5 ± 4.85	-0.79 ± 7.0	4.35 ± 8.3
4	Sathyapalan et al. 2018 [18]	RCT	200	Snack bar; 7.5 g soy protein powder + 33 mg isoflavones 2x daily	Snack bar placebo without isoflavone 2x daily	6 months	0.09 ± 0.7	0.09 ± 0.9	-0.15 + 0.6	-0.10 + 0.7	-0.05 ± 0.36	-0.23 ± 0.39	0.0 + 0.0	0.2 ± 0.07
5	Hong et al. 2021 [26]	RCT	48	100 g dried plums/day	0 g/day	6 months	-12 + 2.1	-2.1 + 1.4	-18.9 + 2.1	-0.3 + 1.9	3.7 + 4.6	-1.1 + 2.5	-58.9 + 9.6	-3.8 + 4.8
6	Braxas et al. 2019 [10]	RCT	54	2 genistein capsules daily for	2 placebo capsules daily	12 weeks	-35.28 + 11.2	-1.23+3.09	-3.5+1.3	-1.18 + 3.1	4.39 + 0.62	0.8 + 1.53	-9.67 + 8.15	-1.26 + 4.95
7	Rezasoltani et al. 2021 [16]	RCT	83	Vitamin E capsule (400 IU/day)	Placebo capsule	4 weeks	−6.50 ± 8.3	3.40 + 6.2	0.00 ± 3.9	5.34 ± 2.2	2.01 ± 4.07	−0.65 ± 2.09	-3.37 + 3.08	6.06 ± 4.43
8	Tadayon et al. 2018 [20]	RCT	100	Two capsules (400 mg) of green tea extract 2x daily	Placebo capsule	4 weeks	-35.1 + 27.6	-13.1 + 25.7	-	-	1 + 8.5	0.6 + 8.2	-18.1 + 26.4	-5 + 29.3