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

Systematic Reviews and Meta-Analysis

Exploring Resveratrol Intervention in Managing Menopausal Symptoms: A Comprehensive Systematic Review of Clinical Trials

Bernadine Tiara Maharani*, Muhammad Daffa Naufal, Hervani Putri, Wahidatur Rosyidah, Leny Silviana Farida

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

ARTICLE HISTORY
Received: 3 April 2024
Revised: 16 May 2024
Accepted: 24 June 2024

CORRESPONDING AUTHOR*
Bernadine Tiara Maharani
bernadinetiaram@gmail.com
Faculty of Medicine Universitas Brawijaya/
dr. Saiful Anwar General Hospital, Malang,
East Java, Indonesia

KEYWORDS
Menopause Symptoms; Post-menopausal; Resveratrol; Management

ABSTRACT

Introduction: Menopause, a significant event in a woman's reproductive lifespan, entails hormonal changes and a range of symptoms affecting various bodily systems. Conventional treatments like hormone replacement therapy (HRT) have limitations and associated risks, prompting interest in alternative therapies such as resveratrol.

Materials/Methods: The literature search was conducted in six databases. The outcome of interest measures the mean changes in bone mineral density (BMD), Quality of Life (QoL), bone biomarkers, menopause symptoms, and cognitive and mood functions pre- and post-interventions. Resveratrol was administered in various forms and doses, including trans-resveratrol 75 mg twice or once daily, 250/500/1000 mg resveratrol tablets, and a combination of fermented soy containing 10 mg equol and 25 mg resveratrol. Quality appraisal was done using the Cochrane Risk of Bias Tool 2.

Results: Resveratrol supplementation in post-menopausal women, involving 745 participants across various studies, has shown remarkable health benefits. These include improved cerebral vasoreactivity (CVR) to hypercapnia, a 10% decrease in overall pain, and enhanced quality of life. Additionally, resveratrol boosts flow-mediated dilation (FMD) by 23% and increases serum sex hormone-binding globulin (SHBG) concentrations by 10%, benefiting bone mineral density (BMD). Over the long term, it leads to a significant 35% increase in FMD and a substantial 33% enhancement in overall cognitive performance, highlighting its diverse benefits.

Conclusion: For women in the post-menopausal stage, resveratrol supplementation shows potential for improving cardiovascular health, relieving pain, enhancing quality of life, supporting bone health, boosting cognitive function, and promoting overall mental well-being.

Cite this as: Maharani, BT, Naufal, MD, Putri H, Rosyidah W, Farida LS (2024) Exploring Resveratrol Intervention in Managing Menopausal Symptoms: A Comprehensive Systematic Review of Clinical Trials. *Asian J Heal Res.* 3 (2): 171–182. doi: 10.55561/ajhr.v3i2.162

INTRODUCTION

Menopause represents a fundamental biological event in the reproductive lifespan of women, denoted by the permanent cessation of menstruation due to ovarian follicular depletion and hormonal alterations, primarily involving declines in estrogen and progesterone levels [1]. Typically occurring in the late 40s to early 50s, menopause initiates a cascade of physiological changes encompassing various bodily systems. These changes manifest clinically as a spectrum of symptoms, including vasomotor symptoms like hot flashes and night sweats, genitourinary symptoms such as vaginal dryness and dyspareunia, as well as mood disturbances and sleep disturbances [2]. While menopause is a universal phenomenon, the presentation and severity of symptoms exhibit significant interindividual variability influenced by genetic predispositions, environmental

factors, and lifestyle choices. However, there are still no specific and highly efficient medical interventions to alleviate these symptoms and treat the clinical consequences of an estrogen-deficient state associated with menopause [3,4].

Conventional treatments for menopause, including hormone replacement therapy (HRT) and non-hormonal medications, present several limitations that warrant consideration. Hormone replacement therapy, comprising estrogen and sometimes progesterone, has been linked to heightened risks of conditions such as breast cancer, heart disease, stroke, and blood clots, underscoring concerns about its long-term safety profile [5,6]. Moreover, both hormonal and non-hormonal treatments may evoke side effects ranging from bloating and breast tenderness to mood swings and sexual dysfunction, affecting treatment adherence and quality of life [5,7]. Additionally, the efficacy of these conventional approaches varies among individuals, with some women experiencing significant symptom relief while others observe limited improvement. Despite primarily targeting common symptoms like hot flashes and vaginal dryness, these treatments may overlook other menopausal manifestations such as mood disturbances and cognitive changes [1,8]. Furthermore, accessibility and cost considerations pose barriers to treatment initiation and continuity, potentially limiting healthcare options for certain populations. Given these limitations, there is a growing interest in exploring alternative therapies, including natural remedies such as resveratrol, to minimize side effects [9,10].

Resveratrol, a natural polyphenol abundant in various plant sources, exhibits antioxidant, anti-inflammatory, and estrogenic properties, thus prompting investigation into its potential efficacy in ameliorating menopausal symptoms, including hot flashes, night sweats, vaginal dryness, and mood disturbances, through modulation of hormone levels and neuroendocrine pathways, alongside its purported benefits in enhancing vascular function and bone density, highlighting its promising role as a complementary therapy in managing menopause-related concerns [11–13]. Recent studies have shown promising results, with research demonstrating that resveratrol supplementation may reduce the frequency and severity of menopausal symptoms in post-menopausal women. However, further large-scale clinical trials are warranted to validate these findings and elucidate the optimal dosage and duration of treatment [9,11,14,15].

Currently, there is a lack of systematic reviews that comprehensively evaluate the potency of resveratrol in alleviating menopausal symptoms, particularly with randomized controlled trials design [16]. Given the current lack of comprehensive understanding regarding the potency of resveratrol in menopausal women, these comprehensive systematic reviews aim to bridge this gap by investigating its effects in pre-, peri-, and post-menopausal women. Therefore, we utilized the most recent relevant randomized controlled trials (RCTs) to conduct this systematic review, aiming to explore the potential of resveratrol in managing menopause symptoms by assessing bone mineral density, bone biomarkers, quality of life, menopausal symptoms, cognitive function, and mood.

MATERIALS/METHODS

This review was based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [17].

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. Various stages of menopause, including pre-, peri, and post-menopausal women, were included in the sample population. As part of the intervention, the patients received resveratrol in various forms and doses, including trans-resveratrol 75 mg twice or once daily, 250/500/1000mg resveratrol tablet, and a combination of fermented soy containing 10 mg equol and 25 mg resveratrol. The PICOS framework is used for inclusion criteria consisting of 1) Population: Pre-, peri-, and post-menopausal women patients; 2) Intervention: Resveratrol or resveratrol enriched foods; 3) Comparison: patients treated with conventional therapy or placebo group; 4) Outcome: Bone mineral density, bone biomarkers, quality of life, menopausal symptoms, cognitive and mood function; 5) Study design: Clinical trial or 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.

Search Strategy

From February 12 to March 8, 2024, three independent researchers searched the literature. Numerous databases were utilized, such as ScienceDirect, PubMed, EbscoHost, ProQuest, SpringerLink, and the Cochrane Journal. The keywords used ("Resveratrol" OR "Trans Resveratrol" OR "Red Grapes" OR "Berries" OR "Dark Chocolate" OR "Peanuts") AND ("Post-menopausal" OR "Climacteric" OR "Perimenopause) AND ("Bone mineral density" OR "bone biomarkers" OR "quality of life" OR "menopausal symptoms" OR "cognitive function").

Data Extraction and Analysis

Three authors 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 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 to assess the risk of bias in the chosen studies. The other writers oversaw the procedure. The instrument takes into 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].

Intervention of Interest

According to recent research, resveratrol, derived from plants, shows promise in relieving menopause symptoms and enhancing well-being by mimicking estrogen, possessing antioxidant and anti-inflammatory qualities, and promoting bone health, cognitive function, and mood [19–21]. In the past decade, researchers have increasingly focused on exploring the connection between resveratrol and the amelioration of menopause symptoms. Therefore, this review focuses on exploring the potential of resveratrol in alleviating menopausal symptoms. A study was conducted to determine their efficacy in increasing patients' Bone mineral density, quality of life, cognitive and mood function.

Outcome of Interest

The mean changes in bone mineral density (BMD), Quality of Life (QoL), bone biomarkers, menopause symptoms, and cognitive and mood functions 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 to thoroughly elucidate the efficacy of resveratrol as a low-side-effect alternative therapy for menopausal women.

RESULTS

Study Selection and Identification

After the literature search, 1.700 articles were published in the last ten years in six databases. Several articles were excluded due to duplication of studies (n = 62). There are 1.532 articles excluded due to ineligible data, such as review articles and books, and inaccessible articles due to subscriptions. Then, many journals do not adhere to the intended study design with inclusion criteria (n = 96). Fig.1 shows the PRISMA flowchart. Thus, 10 articles were included in the systematic review to analyze descriptively.

Risk of Bias Assessment

Based on the risk of bias assessment, four studies have an unclear risk of bias because of ambiguous statements and explanations about the methods used in the studies, which means they did not comply with the requirements of the first, second, and fifth domains of the Cochrane Risk of Bias Tool 2. The remaining studies are thought to have a low-risk bias (Table 1). Most of the data examined have been covered in detail despite the included studies' varied bias levels. Reviewers concluded that the data were appropriate enough for this analysis.

Summaries of the Included Studies

This review included ten studies with randomized controlled trial design (n=9) and pilot clinical trial design (n=1). The resveratrol interventions are used in various forms and doses, including trans-resveratrol 75 mg twice or once daily, 250/500/1000mg resveratrol tablet, and a combination of fermented soy containing 10 mg equol and 25 mg resveratrol. A total of 745 patients with menopause condition were included as participants. All of the participants were in the post-menopausal stage, with a range of ages 52 to 66 years old. The duration of the intervention ranges from 12 weeks to 24 months. The outcomes analyzed in these studies encompassed various aspects of health, including pain intensity, quality of life, cerebrovascular function, blood pressure, arterial compliance, flow-mediated dilatation, hormone levels (estradiol, estrone, testosterone, SHBG), bone health (BMD and turnover biomarkers), cognitive performance, cardiometabolic markers, and mental well-being indicators such as HRQoL, depressive symptoms, and sleep disorders. Table 2 displays the studies that were included.

Descriptive Analysis of Resveratrol's Effectiveness

Several studies have highlighted the beneficial effects of resveratrol supplementation in various health aspects. Wong et al. (2017) demonstrated a significant improvement in cerebral vasoreactivity (CVR) to hypercapnia after 14 weeks of resveratrol supplementation compared to placebo, with a notable reduction in overall pain by 10%. This improvement in pain was found to correlate with the change in CVR to hypercapnia, underscoring the potential link between vascular function and pain management. Additionally, improvements in quality of life (QoL) and total well-being were significantly associated with changes in CVR

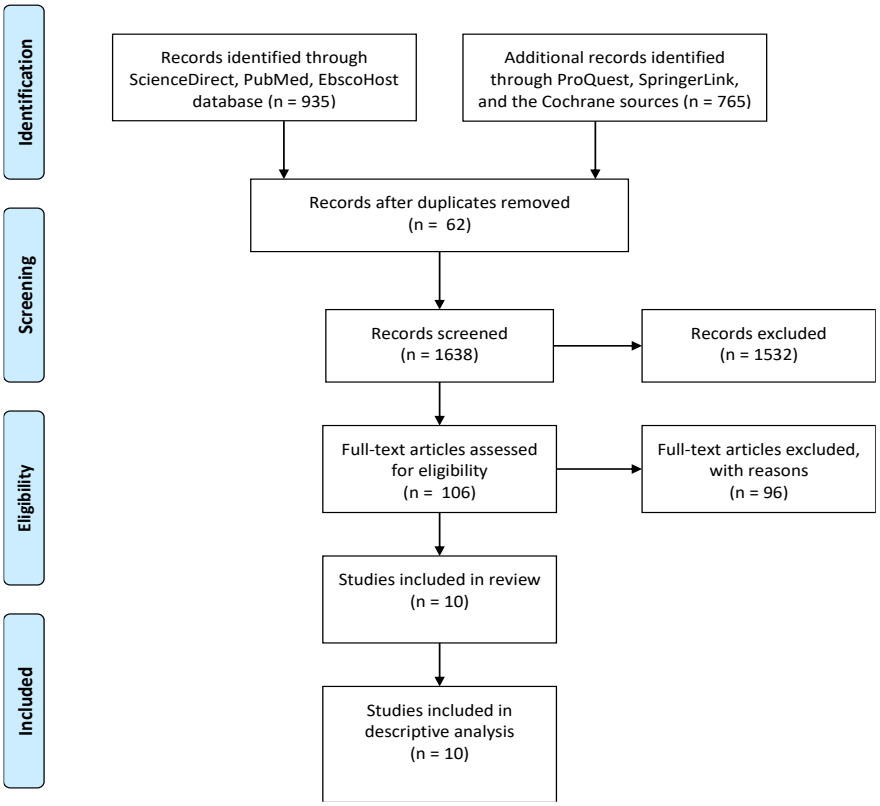

Fig.1. PRISMA Flowchart

to hypercapnia. Wong et al. (2014) reported a 23% relative increase in flow-mediated dilation (FMD) with resveratrol supplementation, along with improvements in cognitive function. Furthermore, Ozemek et al. (2020) found no adverse effects associated with resveratrol supplementation post-exercise, highlighting its safety profile.

On the other hand, studies have also investigated the impact of resveratrol on hormonal markers and bone health. Chow et al. (2014) observed a significant increase in serum sex hormone-binding globulin (SHBG) concentrations and urinary levels of certain markers following resveratrol intervention. Corbi et al. (2023) reported significant improvements in bone mineral density (BMD) associated with resveratrol supplementation, particularly emphasizing the role of bone alkaline phosphatase (BAP) as a predictor of BMD change. Moreover, Wong et al. (2020) noted enhancements in lumbar spine BMD with resveratrol, with potential synergistic effects when combined with calcium and vitamin D supplementation. Overall, these findings underscore the multifaceted benefits of resveratrol across various physiological domains, from vascular health and pain management to hormonal regulation and bone density.

DISCUSSION

Menopause represents a complex physiological transition in a woman's life, involving intricate hormonal changes and adaptations [22]. The decline in estrogen and progesterone levels, coupled with alterations in other hormones such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), triggers the cessation of menstrual cycles [16,23]. This hormonal fluctuation can lead to a wide range of physical symptoms, including hot flashes, night sweats, vaginal dryness, and urinary tract changes. Additionally, menopause is often accompanied by psychological symptoms such as mood swings, anxiety, and depression, as well as cognitive changes like memory lapses and difficulty concentrating [8,14,24]. Beyond its immediate symptomatic manifestations, menopause also presents long-term health implications. The decline in estrogen levels can increase the risk of conditions such as osteoporosis, cardiovascular disease, and cognitive decline [14,25].

Moreover, menopause may influence metabolic processes, leading to changes in body composition, lipid profile, and insulin sensitivity. The overall impact of menopause on a woman's health and well-being

underscores the importance of comprehensive management strategies that address both symptomatic relief and long-term health considerations. As our understanding of menopause continues to evolve, there is a growing emphasis on holistic approaches that encompass lifestyle modifications, dietary interventions, complementary therapies, and, potentially, novel pharmacological agents like resveratrol [13]. By addressing the multifaceted nature of menopause, healthcare providers can better support women through this significant life transition, promoting optimal health and well-being in the menopausal years and beyond [1,26,27].

In this study, resveratrol has demonstrated various health benefits across various physiological systems, supported by empirical evidence. In cardiovascular health, resveratrol notably improved cerebrovascular reactivity (CVR) to hypercapnia, with the resveratrol group showing a significant 7% increase compared to placebo, indicating enhanced vascular function [9,11,14]. Additionally, improvements in flow-mediated dilation (FMD) following resveratrol supplementation further underscore its potential in mitigating endothelial dysfunction, with FMD increasing by 1.38% in the resveratrol group, representing a 23% relative increase [9,11]. These findings suggest resveratrol's potential as a cardiovascular protective agent, potentially reducing the risk of cardiovascular events. Moreover, resveratrol exhibited promising outcomes in pain management and quality of life enhancement. Notably, resveratrol supplementation led to a 10% significant reduction in overall pain levels, correlating positively with improvements in CVR to hypercapnia [7,26,28]. Furthermore, improvements in quality of life and total well-being significantly correlated with changes in CVR, with respective correlation coefficients of 0.382 and 0.453, indicating its potential as an adjunctive treatment for improving overall health outcomes. These correlations highlight the interconnectedness of vascular health and overall well-being, emphasizing the importance of interventions targeting vascular function in promoting holistic health during the menopausal transition [29,30].

In addition to cardiovascular and pain management benefits, resveratrol positively affected bone health, cognitive function, and mental well-being. Significant improvements in bone mineral density (BMD) and bone turnover markers, such as osteocalcin and bone-specific alkaline phosphatase (BAP), were observed following resveratrol supplementation, suggesting a potential role in preventing osteoporosis [4,31]. Moreover, resveratrol demonstrated cognitive benefits, including cognitive performance, memory improvements, and positive neurovascular changes. Its efficacy in alleviating menopausal symptoms, reducing depressive symptoms, and improving sleep quality and anxiety levels further highlights its broad therapeutic potential across multiple health domains [1,24].

Resveratrol, derived from various plant sources, demonstrates promising therapeutic potential in alleviating menopausal symptoms through diverse mechanistic pathways. Its estrogenic activity involves binding to estrogen receptors, mimicking endogenous estrogen effects, thereby mitigating symptoms such as hot flashes, vaginal dryness, and mood disturbances [19,29]. Additionally, resveratrol's antioxidative properties facilitate the scavenging of free radicals, thus reducing oxidative stress and associated inflammation common in menopause. Furthermore, resveratrol modulates signaling pathways involved in bone metabolism, fostering bone health and potentially decreasing osteoporosis risk [12,32]. Moreover, its neuroprotective effects may bolster cognitive function and mood regulation, further relieving menopausal symptoms. These insights underscore the multifaceted mechanisms through which resveratrol acts, suggesting its potential as a therapeutic agent in managing menopause effectively.

Expanding upon its mechanisms, resveratrol's actions extend to key inflammatory pathways like NF-κB and MAPK, exerting robust anti-inflammatory effects. By dampening pro-inflammatory cytokine levels and inhibiting mediator expression, resveratrol attenuates the inflammatory milieu associated with menopause, thus alleviating joint pain and mood disturbances [15,32]. Furthermore, its influence on bone health transcends estrogenic effects, as resveratrol promotes osteoblast function while inhibiting osteoclast activity, favoring bone formation and remodeling. Additionally, resveratrol enhances the expression of genes involved in bone matrix synthesis and mineralization, culminating in improved bone mineral density and reduced osteoporosis susceptibility among menopausal women [4,31,33]. These intricate mechanisms underscore resveratrol's potential as a versatile therapeutic agent in managing various aspects of menopausal symptoms, warranting further exploration in both research and clinical contexts.

Several biases in the included studies can be attributed to the small sample size and the use of different resveratrol doses and forms. The authors were aware of the study's limitations, primarily due to clinical heterogeneity caused by differences in the therapeutic regimens, such as dosages, preparations, administration intervals, and analyzed outcomes. Further research is needed to elucidate the optimal dosage, duration, and safety profile of resveratrol supplementation, specifically for menopausal women. Addressing challenges related to resveratrol's bioavailability and pharmacokinetics is crucial for translating these promising findings into effective clinical interventions for menopause management.

CONCLUSION

In conclusion, these studies underscore the promising potential of resveratrol supplementation across various health domains, particularly in menopausal women. Resveratrol significantly improves cardiovascular health, pain management, and quality of life, with positive correlations between its effects and vascular function enhancement. Additionally, resveratrol shows favorable impacts on bone health, cognitive function, and mental well-being, which are particularly relevant for menopausal women at risk of osteoporosis and cognitive decline. However, standardized protocols for resveratrol intervention are needed to fully understand its therapeutic benefits and optimize its clinical application in this population. Further research focusing on consistent preparations, dosages, administration intervals, and biomarker analysis is crucial to elucidate the full potential of resveratrol supplementation in improving the health outcomes of 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 Sups.FER is responsible 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. Santoro N, Epperson CN, Mathews SB. Menopausal Symptoms and Their Management. Endocrinol Metab Clin North Am. 2015;44(3):497–515.
2. Bansal R, Aggarwal N. Menopausal hot flashes: A concise review. J Midlife Health. 2019;10(1):6–13.
3. D. SK, P. S, G. UR. Health Benefits of Resveratrol. Int J Pharm Sci Nanotechnol. 2009;2(1):407–12.
4. Brown K, Theofanous D, Britton RG, Aburido G, Pepper C, Sri Undru S, et al. Resveratrol for the Management of Human Health: How Far Have We Come? A Systematic Review of Resveratrol Clinical Trials to Highlight Gaps and Opportunities. Int J Mol Sci. 2024;25(2).
5. Mobasheri A, Shakibaei M. Osteogenic effects of resveratrol in vitro: Potential for the prevention and treatment of osteoporosis. Ann N Y Acad Sci. 2013;1290(1):59–66.
6. Thaung Zaw JJ, Howe PRC, Wong RHX. Post-menopausal health interventions: Time to move on from the Women's Health Initiative? Ageing Res Rev [Internet]. 2018;48(September):79–86. Available from: https://doi.org/10.1016/j.arr.2018.10.005
7. Thaung Zaw JJ, Howe PR, Wong RH. Long-term effects of resveratrol on cognition, cerebrovascular function and cardio-metabolic markers in post-menopausal women: A 24-month randomised, double-blind, placebo-controlled, crossover study. Clin Nutr [Internet]. 2021;40(3):820–9. Available from: https://doi.org/10.1016/j.clnu.2020.08.025
8. KOTUSIEWICZ, Wiktoria, SIEKIERKO, Nikola, ŻOŁNIEREK, Maja, LEWANDOWSKI, Mateusz, GACOŃ, Ewa, ZEMBALA, Julita, ZAPAŁA, Brygida, ZĄBER, Aldona, KUCHARSKI, Jakub & ŚWIĘTOCHOWSKI, Jakub. TheKOTUSIEWICZ, Wiktoria, SIEKIERKO, Nikola, ŻOŁNIEREK, Maja, LEWANDOWSK JT. The influence of phytoestrogens on alleviating symptoms associated with menopause. J Educ Heal Sport. 2023;38(1):11–22.
9. Ozemek C, Hildreth KL, Blatchford PJ, Joseph Hurt K, Bok R, Seals DR, et al. Effects of resveratrol or estradiol on postexercise endothelial function in estrogen-deficient post-menopausal women. J Appl Physiol. 2020;128(4):739–47.
10. Evans HM, Howe PRC, Wong RHX. Clinical evaluation of effects of chronic resveratrol supplementation on cerebrovascular function, cognition, mood, physical function and general well-being in post-menopausal women—rationale and study design. Nutrients. 2016;8(3).
11. Wong RHX, Berry NM, Coates AM, Buckley JD, Bryan J, Kunz I, et al. Chronic resveratrol consumption improves brachial flow-mediated dilatation in healthy obese adults. J Hypertens. 2014;31(9):1819–27.
12. Zhang LX, Li CX, Kakar MU, Khan MS, Wu PF, Amir RM, et al. Resveratrol (RV): A pharmacological review and call for further research. Biomed Pharmacother [Internet]. 2021;143(October):112164. Available from: https://doi.org/10.1016/j.biopha.2021.112164
13. Pannu N, Bhatnagar A. Resveratrol: from enhanced biosynthesis and bioavailability to multitargeting chronic diseases. Biomed Pharmacother [Internet]. 2019;109(August 2018):2237–51. Available from: https://doi.org/10.1016/j.biopha.2018.11.075
14. Wong RHX, Evans HM, Howe PRC. Resveratrol supplementation reduces pain experience by post-menopausal women. Menopause. 2017;24(8):916–22.
15. Zern TL, Wood RJ, Greene C, West KL, Liu Y, Aggarwal D, et al. Grape polyphenols exert a cardioprotective effect in pre- and post-menopausal women by lowering plasma lipids and reducing oxidative stress. J Nutr [Internet]. 2005;135(8):1911–7. Available from: https://doi.org/10.1093/jn/135.8.1911
16. Zaw JJT, Howe PRC, Wong RHX. Does phytoestrogen supplementation improve cognition in humans? A systematic review. Ann N Y Acad Sci.

2017;1403(1):150–63.

17. 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.
18. Jørgensen L, Paludan-Müller AS, Laursen DRT, Savović J, Boutron I, Sterne JAC, et al. Evaluation of the Cochrane tool for assessing risk of bias in randomized clinical trials: Overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews. Syst Rev. 2016;5(1):1–13.
19. Pezzuto JM. Resveratrol: Twenty years of growth, development and controversy. Biomol Ther. 2019;27(1):1–14.
20. Lephart ED. Phytoestrogens (Resveratrol and equol) for estrogen-deficient skin—controversies/misinformation versus anti-aging in vitro and clinical evidence via nutraceutical-cosmetics. Int J Mol Sci. 2021;22(20).
21. Sovak M. Grape extract, resveratrol, and its analogs: A review. J Med Food. 2001;4(2):93–105.
22. Aninye IO, Laitner MH, Chinnappan S. Menopause preparedness: Perspectives for patient, provider, and policymaker consideration. Menopause. 2021;28(10):1186–91.
23. Chow HHS, Garland LL, Heckman-Stoddard BM, Hsu CH, Butler VD, Cordova CA, et al. A pilot clinical study of resveratrol in post-menopausal women with high body mass index: Effects on systemic sex steroid hormones. J Transl Med. 2014;12(1):1–7.
24. Davinelli S, Scapagnini G, Marzatico F, Nobile V, Ferrara N, Corbi G. Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized, placebo-controlled study. Maturitas [Internet]. 2017;96:77–83. Available from: http://dx.doi.org/10.1016/j.maturitas.2016.11.016
25. Wong RHX, Thaung Zaw JJ, Xian CJ, Howe PRC. Regular Supplementation With Resveratrol Improves Bone Mineral Density in Post-menopausal Women: A Randomized, Placebo-Controlled Trial. J Bone Miner Res. 2020;35(11):2121–31.
26. Evans HM, Howe PRC, Wong RHX. Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; a 14-week randomised placebo-controlled intervention trial. Nutrients. 2017;9(1).
27. Wada-Hiraike O. Benefits of the Phytoestrogen Resveratrol for Perimenopausal Women. Endocrines. 2021;2(4):457–71.
28. Zaw JJT, Howe PRC, Wong RHX. Sustained cerebrovascular and cognitive benefits of resveratrol in post-menopausal women. Nutrients. 2020;12(3):1–14.
29. Ramírez-Garza SL, Laveriano-Santos EP, Marhuenda-Muñoz M, Storniolo CE, Tresserra-Rimbau A, Vallverdú-Queralt A, et al. Health effects of resveratrol: Results from human intervention trials. Nutrients. 2018;10(12):1–18.
30. Smoliga JM, Baur JA, Hausenblas HA. Resveratrol and health - A comprehensive review of human clinical trials. Mol Nutr Food Res. 2011;55(8):1129–41.
31. Corbi G, Nobile V, Conti V, Cannavo A, Sorrenti V, Medoro A, et al. Equol and Resveratrol Improve Bone Turnover Biomarkers in Post-menopausal Women: A Clinical Trial. Int J Mol Sci. 2023;24(15).
32. Di Credico A, Gaggi G, Izzicupo P, Bucci I, Di Baldassarre A. Resveratrol enhances the cytotoxic activity of lymphocytes from menopausal women. Antioxidants. 2021;10(12).
33. Lai CY, Yang JY, Rayalam S, Della-Fera MA, Ambati S, Lewis RD, et al. Preventing bone loss and weight gain with combinations of vitamin d and phytochemicals. J Med Food. 2011;14(11):1352–62.

Table.1. Cochrane Risk of Bias Tool 2 for Randomized Controlled Trial Studies

No	Study (year)	Study Design	D1	D2	D3	D4	D5	Overal Risk of Bias
1	Wong et al., 2017 [11]	RCT						5/5 Low Risk of Bias
2	Wong et al., 2014 [17]	RCT						5/5 Low Risk of Bias
3	Ozemek et al., 2020 [9]	RCT						5/5 Low Risk of Bias
4	Chow et al., 2014 [23]	RCT						3/5 Moderate Risk of Bias
5	Corbi et al., 2023 [31]	RCT						4/5 Low Risk of Bias
6	Wong et al., 2020 [25]	RCT						5/5 Low Risk of Bias
7	Zaw et al., 2020 [28]	RCT						5/5 Low Risk of Bias
8	Davinelli et al., 2017 [24]	RCT						3/5 Moderate Risk of Bias
9	Evans et al., 2017 [26]	RCT						3/5 Moderate Risk of Bias
10	Zaw et al., 2021 [28]	RCT						3/5 Moderate Risk of Bias

Table 1. Summaries Included Studies

No.	Study (Year)	Study Design	Duration	Intervention	Comparison	Sample (n)	Mean age (SD)	Outcomes	Summary of Results	Adverse effects
1	Wong et al., 2017 [11]	RCT	14-weeks	Trans-resveratrol (75 mg, twice daily)	Placebo twice daily	80	61.5±0.9 years	Pain intensity, QoL, cerebrovascular function	▪ Resveratrol supplementation for 14 weeks significantly improved CVR to hypercapnia compared to placebo. Placebo group: 52.4+2.3%; Resveratrol group: 58.1+2.4%; P=0.011. ▪ Resveratrol supplementation reduced overall pain by 10% compared to placebo in ITT and PP analyses. ▪ Improvement in overall pain correlated with the change in CVR to hypercapnia (r=0.405, P=0.004). ▪ Improvements in QoL and total well-being were significantly correlated with changes in CVR to hypercapnia (r=0.382, P=0.007; and r=0.453, P=0.002, respectively).	No adverse effects were reported.
2	Wong et al., 2014 [17]	RCT	12-weeks	Trans-resveratrol (75 mg, once daily)	Placebo once daily	28	61+1.3 years	Blood pressure and arterial compliance, flow-mediated dilatation (FMD), Stroop color-word test	▪ Mean compliance with supplementation: Resveratrol was 98.5+0.5%, placebo was 98.6+0.4%, and no participant had less than 80% compliance. ▪ FMD increased by 1.38+0.57% with resveratrol, a 23% relative increase (d=0.940; 95% CI: 0.22–2.54, P=0.021, paired t-test). This improvement remained significant after adjusting for baseline FMD (95% CI: 0.04–2.72, P=0.044). ▪ A single dose of resveratrol (75mg) post-chronic supplementation resulted in a 1.94+0.56% greater FMD response compared to placebo (35% relative increase; d=1.35; 95% CI: 0.78–3.09, P=0.002). ▪ Participants tended to make 50% fewer uncorrected errors during word reading; however, after adjusting for multiple comparisons, this effect was insignificant (P=0.050).	No adverse events, including serious adverse events, were recorded.
3	Ozemek et al., 2020 [9]	RCT		Single dose, trans-resveratrol (250-mg resveratrol tablet + placebo transdermal patch)	Placebo (inactive transdermal patch + inactive tablet) and estradiol (0.05 mg/day transdermal patch + placebo tablet)	15	58.1±3.1	Improving resting flow-mediated dilation and blood draw after exercise	▪ Postexercise systolic, diastolic, and MAP were similar between placebo and resveratrol conditions at 30, 60, and 120 minutes postexercise. ▪ Estradiol treatment showed significantly lower postexercise 60- and 120-min systolic and diastolic blood pressure than placebo, with 120-min systolic BP also lower than resveratrol. MAP was consistently lower after exercise in the estradiol group compared to resveratrol. ▪ At 60 min after exercise, glucose levels were lower in the estradiol group than resveratrol. ▪ Pre-exercise brachial artery FMD was higher in both resveratrol and estradiol groups compared to placebo. Estradiol concentration was naturally higher in the estradiol group.	N/A

									▪ Postexercise, both percent and absolute brachial artery FMD were greater in resveratrol and estradiol groups compared to placebo at all time points. ▪ Within the placebo group, FMD decreased at 30- and 60-minute post-exercise but normalized at 120-minute post-exercise.	
4	Chow et al., 2014 [23]	Pilot clinical trial	12-weeks	1 gm dose of resveratrol once a day (two 500 mg caplets QD) with	-	40	58±8	change in serum estradiol, estrone, testosterone, SHBG, 2-OHE1/16α-OHE1 ratio levels, and safety profiles.	▪ Baseline serum concentrations: Estradiol 12.3 ± 20.7 pg/ml, Estrone 26.1 ± 12.7 pg/ml, Testosterone 0.18 ± 0.11 ng/ml. Resveratrol intervention didn't significantly alter these sex steroid hormones. ▪ Baseline SHBG concentrations: 42.1 ± 17.6 nmol/L. Resveratrol intervention led to a 10% increase in serum SHBG concentrations ($p < 0.01$). ▪ Baseline urinary levels: 2-OHE1 9.5 ± 8.8 ng/mg creatinine, 16α-OHE1 6.6 ± 6.1 ng/mg creatinine, 2-OHE1/16α-OHE1 1.7 ± 1.4. Resveratrol intervention resulted in a 73.2% increase in urinary 2-OHE1 levels ($p < 0.01$) and an 84.5% increase in the 2-OHE1/16α-OHE1 ratio ($p < 0.01$).	Elevation in hepatic ALT and AST enzymes, skin rash, constipation, diarrhea, shortness of breath, and wheezing.
5	Corbi et al., 2023 [31]	RCT	12 months	200 mg fermented soy containing 10 mg equol and 25 mg resveratrol	Placebo	60	52.09 ± 1.71	Whole-body BMD and bone turnover markers like DPD, TRACP-5b, osteocalcin, and BAP were assessed.	▪ Percentage changes in bone metabolism markers and BMD differed significantly between placebo and active groups: DPD -32.63 ± 12.08%, $p < 0.0001$; TRACP-5b -8.78 ± 9.24%, $p = 0.0331$; osteocalcin +49.70 ± 28.54%, $p < 0.0001$; BAP +8.00 ± 4.64%, $p < 0.0001$; BMD +3.17 ± 2.74%, $p < 0.0001$. ▪ Percentage changes in BAP were the best predictor of BMD change ($\beta = 0.216$, 95% CI 0.0814–0.3498, $p = 0.002$), followed by participation in the active group ($\beta = 3.394$, 95%CI 1.245–5.544, $p = 0.003$), and percentage changes in DPD ($\beta = 0.0516$, 95%CI 0.008–0.095, $p = 0.020$). ▪ In the intervention group, a statistically significant association existed between percentage changes in BAP and BMD ($\beta = 0.337$, 95% CI 0.139–0.536, $p = 0.002$).	None of the subjects experienced serious adverse events.
6	Wong et al., 2020 [25]	RCT	24 months	Trans-resveratrol (75 mg, twice daily)	Placebo twice daily	128	64.3±1.3	BMD values of the dual neck of the femur, cerebrovascular responsiveness (CVR) to hypercapnia	▪ Resveratrol supplementation led to a modest 1.3% increase in lumbar spine BMD compared to placebo, improving the mean T-score by 1.5%. ▪ There was a trend towards reduced CTX levels after 12 months of resveratrol supplementation, while plasma osteocalcin levels remained unaffected. ▪ Resveratrol treatment resulted in significantly higher improvements in lumbar spine and femoral neck BMD and T-score compared to placebo, with lower CTX levels observed. ▪ Spine BMD increased with resveratrol and was greater in those who took calcium or vitamin D and calcium than those who took neither.	Four AE occurred in the resveratrol group but may not be directly attributed to supplementation. These included itching, menses, prolapsed bladder, and a pre-scheduled eye operation.

								▪ The benefits of resveratrol on lumbar spine BMD were enhanced in individuals who were regularly supplemented with vitamin D and calcium compared to those who took calcium alone. ▪ Increases in femoral neck T-score correlated with increases in CVR.	
7	Zaw et al., 2020 [28]	RCT	14-weeks	Trans-resveratrol (75 mg, twice daily)	Placebo twice daily	129	64 ± 1	Systemic Vascular Function Blood, Cognitive Performance, Cerebrovascular Function, Cardiometabolic Markers, Safety Profiles.	▪ Blood pressure and arterial compliance remained unchanged after 12 months of supplementation in both groups. ▪ Resveratrol supplementation improved performance in processing speed and cognitive flexibility tests, leading to a modest increase in overall cognitive performance. ▪ Resveratrol didn't affect CVR to hypercapnia but attenuated a decline in neurovascular coupling capacity, especially in response to cognitive flexibility tests. ▪ There were no significant differences in cardiometabolic markers between placebo and resveratrol groups. Still, reductions in fasting blood glucose were associated with improved overall neurovascular coupling capacity following resveratrol supplementation.	Four adverse events in the resveratrol group, itching, menses, prolapsed bladder, and pre-scheduled left eye operation, were not directly linked to supplementation.
8	Davinelli et al., 2017 [24]	RCT	12-weeks	200 mg of fermented soy containing 10 mg of equol and 25 mg of resveratrol (1 tablet/day)	Placebo (1 tablet/day)	60	52.7 ± 2.1	HRQoL questionnaire Menopause Rating Scale (MRS), depressive symptoms measured by HAM-D, and sleep disorders assessed by NHP	▪ Statistically significant improvement was observed in all symptoms assessed by MRS, with notable reductions in dryness of the vagina (-85.7%), heart discomfort (-78.8%), and sexual problems (-73.3%). ▪ The treatment significantly reduced the number of subjects experiencing depressive symptoms evaluated by HAM-D. ▪ Subjects experiencing loss of interest in work activities decreased by 94.1% after 3 months of treatment, compared to placebo at the same time ($p < 0.001$). ▪ Analysis of NHP revealed significant improvement, especially in sleep quality ($p < 0.001$), among subjects receiving active treatment compared to the placebo group over time.	The treatment was well tolerated, and no adverse events were reported during the study.
9	Evans et al., 2017 [26]	RCT	14-weeks	Trans-resveratrol (75 mg, twice daily)	Placebo twice daily	80	61.5 ± 1.1	Cognitive Performance, Cerebrovascular Function, and Mood	▪ The resveratrol group outperformed placebo in all cognitive tasks based on Z-scores, showing significant improvements in overall cognitive performance ($p = 0.003$; Cohen's $d = 0.69$), semantic ($p = 0.043$; Cohen's $d = 0.48$), and verbal memory ($p = 0.043$; Cohen's $d = 0.48$). ▪ After adjusting for depressive symptoms, only verbal memory ($p = 0.037$) and overall cognitive performance ($p = 0.023$) remained significantly improved by resveratrol. ▪ Resveratrol supplementation significantly improved CVR to hypercapnia by 7% compared to placebo ($p = 0.010$; Cohen's $d = 0.69$).	N/A

									▪ CVR to the cognitive test battery was also enhanced by resveratrol ($p = 0.002$; Cohen's $d = 0.71$), and differences in CVR correlated significantly with differences in overall cognitive performance. ▪ Resveratrol supplementation led to a significant reduction in anxiety ($p = 0.025$; Cohen's $d = 0.50$).	
10	Zaw et al., 2020 [28]	RCT	24 months	Trans-resveratrol (75 mg, twice daily)	Placebo twice daily	125	66 ± 8	Cognitive Performance, Cerebrovascular Function, and Cardiometabolic measurements	▪ Resveratrol supplementation showed a significant 33% improvement in overall cognitive performance. ▪ Resveratrol significantly improved specific cognitive tasks: the Dimensional Change Card Sort Test by 113% and the Forward Spatial Span Test by 208%. ▪ In women over 65 (late-life), there was a relative improvement in verbal memory with resveratrol. ▪ Resveratrol significantly improved resting mean CBFV by 8% and CVR to hypercapnia by 12%. ▪ Overall, neurovascular coupling was enhanced by 7% with resveratrol, especially during tests of cognitive flexibility. ▪ Resveratrol reduced fasting insulin levels by 9%. ▪ Improvement in CVR to hypercapnia with resveratrol correlated significantly with improvement in cognitive flexibility.	Two adverse events in the resveratrol group: exacerbated gastric reflux and pre-scheduled heart valve stent surgery. These may not be directly linked to the supplementation.