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

Systematic Review

L-Citrulline Supplementation in Postmenopausal Women: Evidence from Clinical Trials

Laily Arifianti*, Intan Mumtazah, Satya Panggabean, Rajasawardana Muhammad

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

ARTICLE HISTORY
Received: 21 May 2025
Revised: 28 June 2025
Accepted: 23 July 2025

CORRESPONDING AUTHOR*
Laily Arifianti
lailynurrachmah263@gmail.com
Faculty of Medicine, Universitas Brawijaya/
Dr. Saiful Anwar General Hospital, Malang,
East Java, Indonesia

KEYWORDS
L-Citrulline; Postmenopausal Women; Vascular Function; Endothelial Dysfunction; Muscle Oxygenation

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ABSTRACT

Introduction: Postmenopausal women are at heightened risk for cardiovascular and muscular health decline due to endothelial dysfunction, arterial stiffness, and reduced nitric oxide (NO) bioavailability. L-Citrulline, a precursor to L-arginine and NO, has emerged as a promising supplement to counter these age-related vascular and musculoskeletal impairments.

Material and Methods: A systematic review of randomized controlled trials was conducted in accordance with PRISMA guidelines using PubMed, ScienceDirect, and Cochrane Library databases. Eligible studies assessed oral L-Citrulline supplementation in postmenopausal women, with outcomes categorized into: vascular function (blood pressure, flow-mediated dilation [FMD], pulse wave velocity [PWV]); muscle function and oxygenation (tissue saturation index [TSI], oxy-/deoxyhemoglobin [O_2Hb/HHb], strength, lean mass, exercise performance); and autonomic regulation (heart rate variability [HRV]). Methodological quality was evaluated using the Cochrane Risk of Bias Tool 2.0.

Results: L-Citrulline supplementation, administered in doses ranging from 6 to 10 g/day over 4–8 weeks, significantly improved cardiovascular outcomes, including reductions in brachial and aortic systolic/diastolic blood pressure, pulse pressure, and augmentation index. Flow-mediated dilation (FMD) improved by up to 2.7%, and nitric oxide availability increased, indicating enhanced endothelial function. Additionally, L-Citrulline improved muscle oxygenation during exercise, increased leg lean mass and strength when combined with low-intensity resistance training, and favorably modulated autonomic function through improved heart rate variability.

Conclusion: L-Citrulline supplementation demonstrates substantial potential for improving vascular health, enhancing muscle oxygenation and strength, and restoring autonomic balance in postmenopausal women. These findings support its use as a non-pharmacological strategy to mitigate age-related declines in cardiovascular and muscular function.

Cite this as: Arifianti L, Mumtazah I, Panggabean S, Muhammad R (2025) L-Citrulline Supplementation in Postmenopausal Women: Evidence from Clinical Trials. *Asian J Heal Res*. 4 (2): 99–108. doi: 10.55561/ajhr.v4i2.256

INTRODUCTION

Aging in women is strongly associated with an increased incidence of cardiovascular disease (CVD), particularly after menopause [1]. In the United States, around 75% of women aged 65–75 and 78% of those over 75 are hypertensive [2,3]. Compared to men, women with hypertension tend to have a higher burden of cardiometabolic risk factors, including abdominal obesity and elevated cholesterol levels, and often experience less effective blood pressure control despite antihypertensive treatment [4].

One key factor contributing to this disparity is increased arterial stiffness, which becomes more pronounced in postmenopausal women and is closely linked to elevated systolic blood pressure (SBP) and the development of heart failure with preserved ejection fraction (HFpEF) [4,5]. This vascular stiffening is often preceded by endothelial dysfunction, characterized by reduced nitric oxide (NO) bioavailability due to limited availability of L-arginine (ARG), the main substrate for NO production [6,7]. Moreover, emerging studies suggest that vascular dysfunction and increased arterial stiffness may negatively affect skeletal muscle health,

contributing to lower lean mass and reduced strength in older women [8].

Despite adequate control of resting blood pressure with medication, many older women with hypertension continue to show exaggerated systolic blood pressure (SBP) responses during even low-intensity physical activity. This heightened response is largely attributed to increased arterial stiffness and overactive sympathetic nervous system signaling, which causes excessive vasoconstriction through muscle mechano- and metaboreceptor activation [2,9]. In postmenopausal women, this effect is more pronounced due to impaired endothelial function and reduced NO bioavailability, which limits the ability of blood vessels to dilate and counteract sympathetic-mediated vasoconstriction. These vascular impairments can compromise muscle blood flow during activity, particularly in the lower limbs, potentially contributing to declines in muscle mass and strength over time [10,11]. Studies have observed a direct relationship between vascular dysfunction and musculoskeletal decline, suggesting that impaired muscle perfusion may be an important factor in age-related muscle loss among hypertensive women [12,13].

L-citrulline (CIT), a naturally occurring amino acid, has emerged as a promising supplement to improve vascular health by increasing plasma L-arginine levels and enhancing NO production [6,14]. Unlike L-arginine, which is rapidly broken down by intestinal and hepatic arginase, CIT bypasses this metabolism and is efficiently converted into L-arginine in the kidneys, resulting in sustained increases in NO availability [7,15]. Short-term supplementation with CIT has been shown to improve endothelial function in older adults and lower both resting and post-exercise blood pressure [13]. In younger adults, 6 grams of daily CIT for two weeks reduced aortic SBP increases during exercise under sympathetic stress [7]. In postmenopausal women, combining CIT supplementation with strength-based interventions such as whole-body vibration training (WBVT) has produced additive benefits, improving aortic stiffness and increasing lower-limb lean mass more effectively than either intervention alone. These findings suggest CIT may support vascular and muscular health through improved endothelial function and nutrient delivery to working muscles [7,16].

Although recent studies highlight the benefits of L-citrulline supplementation in vascular and muscular outcomes, there is still no comprehensive review evaluating its full potential in postmenopausal women. Specifically, the effects of CIT on vascular function (including blood pressure, endothelial function, and arterial stiffness), muscle oxygenation and performance (such as oxygen delivery, muscle strength, and lean mass), and autonomic regulation (measured by heart rate variability) remain poorly summarized. Given the increased cardiovascular and muscular vulnerability in postmenopausal women, a clearer understanding of CIT's therapeutic value is needed. Therefore, this systematic review aims to synthesize findings from recent clinical trials to assess the efficacy of L-citrulline supplementation in improving vascular function, muscle health and oxygenation, and autonomic balance in postmenopausal women.

MATERIAL AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

The inclusion and exclusion criteria were predefined to ensure methodological consistency and reduce selection bias. Eligible studies were clinical trials, including randomized controlled trials and prospective intervention studies, published within the last ten years, and focused on L-Citrulline supplementation in postmenopausal women. The selection was based on the PICOS framework: Population: Postmenopausal women, particularly those with hypertension or impaired vascular function. Intervention: Oral L-Citrulline supplementation, regardless of dosage or duration. Comparison: Placebo or no intervention control groups. Outcomes: At least one vascular-related outcome, including blood pressure, endothelial function, arterial stiffness, muscle oxygenation, aortic pressure, or exercise-related circulatory performance.

Study Design

Human clinical trials (randomized controlled trials, cohort studies, or case-control designs). Studies were excluded if they (1) involved male or pre-/perimenopausal participants without subgroup analysis for postmenopausal women, (2) were animal or in vitro studies, (3) involved combination supplements where the specific effect of L-Citrulline could not be determined, or (4) were not published in English or lacked full-text availability.

Search Strategy

A structured literature search was performed from February 12 to March 8, 2024, using three electronic databases: PubMed, ScienceDirect, and the Cochrane Library. The search was conducted independently by three reviewers to ensure comprehensiveness and minimize bias. The Boolean search terms were as follows: ("L-Citrulline" OR "Citrulline supplementation" OR "Citrulline") AND ("Postmenopausal women" OR "Postmenopause" OR

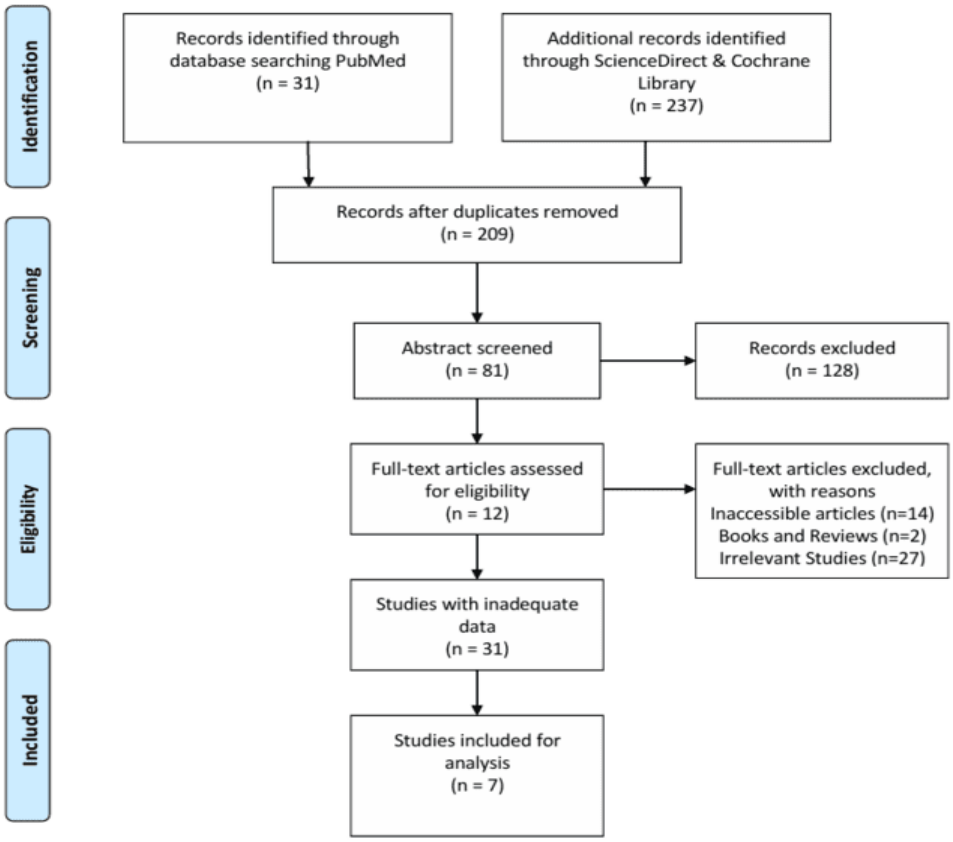


Fig. 1. PRISMA Flowchart

"Menopause") AND ("Blood pressure" OR "Hypertension" OR "Vascular function" OR "Endothelial function" OR "Arterial stiffness" OR "Muscle oxygenation" OR "Aortic pressure" OR "Exercise performance" OR "Cardiovascular health") AND ("Clinical trial" OR "Randomized controlled trial" OR "RCT"). Reference lists of included articles were also manually screened to identify additional relevant studies not captured in the database search.

Data Extraction and Analysis

Relevant data were extracted independently by three reviewers using a standardized data extraction sheet, which included information on authorship, publication year, study design, sample size, participant characteristics, L-Citrulline dosage and duration, control conditions, and reported outcomes. Discrepancies between reviewers were resolved through discussion or by consulting a fourth reviewer if necessary. Extracted data were synthesized qualitatively, and where applicable, summary tables were used to organize findings by outcome domains.

Risk of Bias Assessment

The Cochrane Risk of Bias Tool 2.0 was applied to assess methodological quality of the included randomized controlled trials. The tool evaluates five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each study was classified as having low, some concerns, or high risk of bias. For studies that were not randomized trials, an appropriately adapted risk of bias tool was used where relevant.

Intervention of Interest

L-Citrulline is a non-proteinogenic amino acid involved in nitric oxide production through the L-arginine-NO pathway. It has been proposed as a vascular support supplement, particularly in populations with endothelial dysfunction, such as postmenopausal women. This review focused on the efficacy of oral L-Citrulline supplementation in improving vascular health, examining variations in dose, frequency, and formulation.

Outcomes of Interest

Primary outcomes included vascular-related physiological indicators such as systolic and diastolic blood pressure, endothelial function (e.g., flow-mediated dilation), arterial stiffness (e.g., pulse wave velocity), muscle oxygenation, aortic pressure or wave reflection, and performance-based measures of exercise-related blood flow. These outcomes were selected for their relevance to cardiovascular health in postmenopausal women and their frequent reporting in clinical trials of L-Citrulline.

RESULTS

Study Selection

Following a comprehensive literature search, a total of 268 records were identified—31 articles from PubMed and 237 from ScienceDirect and the Cochrane Library. After removing duplicates, 209 records remained for screening. During the abstract screening phase, 128 records were excluded, leaving 81 articles for further evaluation. Of these, 12 full-text articles were assessed for eligibility. However, 43 full-text articles were excluded due to various reasons, including inaccessible articles (n = 14), books and reviews (n = 2), and irrelevant studies (n = 27). Among the remaining, 31 studies were excluded due to inadequate data, resulting in 7 studies included for final analysis. The study selection process is illustrated in Fig.1.

Risk of Bias Assessment

Based on the Cochrane Risk of Bias 2 (ROB 2) assessment, two of the seven included randomized controlled trials, Maharaj et al. (2022) and Wong et al. (2016), were judged to have a moderate risk of bias [9,17]. This was due to concerns related to domain 2 (deviations from intended interventions) and domain 5 (selection of the reported result), where the studies lacked sufficient detail or clarity in their methodology. The remaining five studies were assessed as having a low risk of bias across all domains, reflecting well-conducted trial designs with transparent reporting. Despite some variability in methodological quality, the overall data from the included studies were deemed appropriate and reliable for further analysis. The risk of bias summary is illustrated in Table 2.

Summaries of the Included Studies

This systematic review included seven studies, all of which employed randomized controlled trial (RCT) designs and involved a total of 172 postmenopausal women, primarily hypertensive or obese, aged between 52 and 66 years. The interventions consisted of oral L-citrulline supplementation, administered either as a single acute dose (6 g) or in chronic regimens ranging from 6 to 10 g per day over durations of 4 to 8 weeks. One study used a crossover design (18), while the remaining studies applied parallel-group randomization, with most utilizing double-blind and placebo-controlled protocols. Several studies also incorporated additional interventions such as whole-body vibration training (WBVT) or low-intensity resistance training (SVLIRT) [7,16]. The outcomes assessed were categorized into three domains: vascular function (six studies), muscle function and oxygenation (three studies), and autonomic regulation (one study). A detailed summary of each study, including design, sample characteristics, intervention details, and targeted outcome domains, is presented in Table 1.

Descriptive Analysis of L-Citrulline Effectiveness

L-Citrulline supplementation has shown consistent benefits in improving vascular function among postmenopausal women, particularly those with hypertension or obesity. Multiple studies reported significant reductions in blood pressure parameters, including brachial and aortic systolic and diastolic BP, pulse pressure (PP), and wave reflection indices such as forward (Pf) and backward (Pb) pressure components. For example, Maharaj et al. (2022) found a reduction in aortic systolic BP and PP following a single 6 g dose of L-Citrulline during exercise [17,18]. A more sustained intervention (10 g/day for 4 weeks) led to a significant decrease in brachial SBP and DBP, and improved flow-mediated dilation (FMD) by Δ1.4 ± 2.0% versus Δ−0.5 ± 1.7% in the placebo group ($p = 0.03$). Kang et al. (2023) also demonstrated a dose-dependent improvement in superficial femoral artery FMD, with Δ1.8 ± 0.3% after 4 weeks and Δ2.7 ± 0.5% after 8 weeks when combined with low-intensity resistance training (SVLIRT) [16,19]. Additionally, L-Citrulline reduced arterial stiffness markers such as carotid-femoral pulse wave velocity (cfPWV), with a trend toward significance ($p = 0.07$), and improved nitric oxide bioavailability, evidenced by increased plasma NOx levels (Wong et al., 2016) [9].

Beyond vascular improvements, L-Citrulline demonstrated promising effects on muscle function, oxygenation, and autonomic regulation. Kang et al. (2024) reported enhanced muscle oxygenation during isometric handgrip exercise, with improved tissue saturation index (TSI), increased oxyhemoglobin (O_2Hb), and reduced deoxyhemoglobin (HHb), indicating better oxygen delivery and utilization [19]. In combination with SVLIRT, L-Citrulline increased leg lean mass by Δ0.49 ± 0.15 kg and leg curl strength by Δ6.9 ± 0.9 kg, significantly outperforming the placebo+SVLIRT group [16]. Wong et al. (2016) found that the combined L-Citrulline and whole-body vibration training (WBVT) intervention significantly

improved augmentation index adjusted for heart rate (AIx@75) by 10.5%, suggesting superior benefits for muscle function and vascular load. Regarding autonomic regulation, Wong et al. (2016) also demonstrated a significant improvement in heart rate variability (HRV), with reductions in sympathetic activity (nLF), enhanced vagal tone (nHF), and decreased LnLF/LnHF ratio, indicating restored sympathovagal balance following 8 weeks of 6 g/day L-Citrulline supplementation [9]. Collectively, these findings underscore L-Citrulline's multifaceted role in promoting cardiovascular health, improving muscular performance, and modulating autonomic function in postmenopausal women.

DISCUSSION

The exaggerated systolic blood pressure (SBP) response during physical activity in postmenopausal women is a clinically significant phenomenon linked to endothelial dysfunction, arterial stiffening, and sympathetic overactivation. During isometric handgrip (IHG) and post-exercise muscle ischemia (PEMI), older women exhibit amplified sympathetic-mediated vasoconstriction without a proportional increase in cardiac output, leading to higher SBP responses compared to younger cohorts [4,8]. This dysregulation is further exacerbated by the natural decline in estrogen post-menopause, which impairs NO-mediated vasodilation. Repeated exposure to such hemodynamic stress may initiate or accelerate vascular remodeling, promoting chronic systolic hypertension and increasing the risk for conditions such as heart failure with preserved ejection fraction (HFpEF) [5]. These findings underscore the critical need for targeted interventions that address the vascular and autonomic impairments specific to this population.

Endothelial dysfunction in postmenopausal women is primarily driven by reduced bioavailability of nitric oxide (NO), reflected in impaired flow-mediated dilation (FMD) and increased pulse wave velocity (PWV) [2,14]. Declines in endothelial responsiveness begin as early as the perimenopausal stage and tend to progress rapidly. L-Citrulline (CIT) supplementation offers a mechanistically grounded intervention by increasing systemic L-arginine availability, the substrate for endothelial NO synthase (eNOS), without being degraded by intestinal or hepatic arginase. CIT is metabolized in the kidneys, resulting in sustained L-arginine levels and enhanced NO production. Moreover, CIT may exert additional benefit by acting as an allosteric inhibitor of arginase, further preserving L-arginine pools. This biochemical advantage may explain why CIT, unlike L-arginine, effectively enhances endothelial function even in populations with established vascular dysfunction, such as hypertensive postmenopausal women [10].

Empirical findings from the included studies provide support for CIT's vascular and muscular benefits in this demographic. Chronic supplementation (4–8 weeks, 6–10 g/day) was associated with improvements in endothelial function, reductions in both aortic and brachial SBP, and increased NOx levels [12,16,19]. Maharaj et al. (2022) demonstrated that CIT attenuated exercise-induced SBP and MAP elevations during sympathetic stress, an effect not seen with acute dosing [17,18]. Kang et al. (2023, 2024) further observed that CIT combined with low-intensity resistance training led to improvements in femoral artery FMD, muscle oxygenation (O_2Hb, TSI), and lower-limb lean mass, suggesting a synergistic interaction between vascular and muscular adaptations. However, in normotensive individuals or those with less sympathetic drive, CIT's effects were more modest, highlighting its context-specific efficacy [16,19]. Additionally, while CIT appeared effective during high-sympathetic load (e.g., exercise + cold pressor), it showed limited impact during milder sympathetic challenges, indicating a threshold-dependent responsiveness [20].

Despite these promising findings, the heterogeneity of study designs, CIT dosing strategies, and sample characteristics limits the generalizability of the conclusions. Many trials included small cohorts and lacked long-term follow-up. Furthermore, variability in baseline vascular status (e.g., normotensive vs. hypertensive participants), the presence of antihypertensive medications, and co-interventions like resistance or vibration training introduce potential confounders. While CIT's biochemical rationale is well-supported, its clinical application requires further clarification of dose-response relationships, optimal treatment durations, and long-term safety, particularly in menopausal populations. Finally, although sex-specific vascular responses were observed in some studies, further mechanistic investigations into hormonal modulation of NO signaling and sympathetic regulation are warranted to optimize personalized interventions for postmenopausal women.

CONCLUSION

Current clinical evidence highlights the promising role of L-Citrulline supplementation in enhancing cardiovascular and muscular health among postmenopausal women. Supplementation has been shown to improve vascular function by reducing blood pressure and enhancing endothelial responsiveness, while also supporting better muscle oxygenation, strength, and autonomic balance. These benefits make

L-Citrulline a valuable non-pharmacological option for addressing age-related vascular and muscular decline.

ACKNOWLEDGMENT

We thank all the authors of the articles reviewed in this article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Availability of Data and Materials

All data sources described in this study are directed to the corresponding author.

Ethics Approval and Consent to Participate

No human subjects are in this article, and informed consent is not applicable.

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Tabel 1. Summaries Included Studies

No	Study	Study Design	Sample	Intervention	Placebo	Duration of Treatment	Outcome Analysis		
							Vascular Function	Muscle Function and Oxygenation	Autonomic Regulation
1	Maharaj et al. (2022) [18]	Randomized, placebo-controlled, crossover trial	15 hypertensive Postmenopausal women	6 g L-citrulline (single dose)	Yes	Acute (single session, crossover with ≥ 3-day washout)	A single 6g dose of L-Citrulline significantly reduced aortic systolic blood pressure (SBP), pulse pressure (PP), and wave reflection components (Pf, Pb) during exercise compared to placebo.	NA	NA
2	Kang et al. (2023) [16]	Randomized, double-blind, placebo-controlled, parallel	24 hypertensive postmenopausal women	10 g/day L-citrulline ± low-intensity resistance training	Yes	4 weeks L-citrulline ± 4 weeks with resistance training (total 8 weeks)	L-Citrulline alone for 4 weeks significantly improved superficial femoral artery FMD by Δ1.8 ± 0.3% (vs −0.2% in placebo); the combination with SVLIRT resulted in Δ2.7 ± 0.5% improvement after 8 weeks (p = 0.003).	L-Citrulline supplementation increased leg lean mass and muscle strength. CIT + SVLIRT group had the greatest improvements compared to CIT or SVLIRT alone. The combination showed additive effects	NA
3	Maharaj et al. (2022) [17]	Randomized, double-blind, placebo-controlled	25 hypertensive postmenopausal women	10 g/day L-citrulline	Yes	4 weeks	10 g/day L-Citrulline significantly reduced brachial systolic and diastolic BP, and improved endothelial function (FMD) in hypertensive postmenopausal women.	NA	NA
4	Dillon et al. (2024) [21]	Randomized, double-blind, placebo-controlled	22 postmenopausal women	10 g/day L-citrulline	Yes	4 weeks	4 weeks of L-Citrulline significantly attenuated the increase in aortic SBP, PP, Pf, and Pb during metaboreflex activation. This suggests reduced arterial stiffness and wave reflection	NA	NA
5	Wong et al. (2016) [22]	Randomized controlled trial	41 obese postmenopausal women	6 g/day L-citrulline ± WBVT	Yes	8 weeks	The study found that all groups (l-citrulline, WBVT + l-citrulline, and WBVT+Placebo) experienced significant decreases in brachial and aortic blood pressures as well as augmentation pressure (AP), while also showing significant increases in plasma nitric oxide metabolites (NOx) after 8 weeks of intervention.	When combined with whole-body vibration training, L- Citrulline improved lower-body muscle strength and lean mass, though effects were not isolated to L-Citrulline alone.	NA
6	Kang et al. (2024) [19]	Randomized, double-blind, placebo-controlled	22 hypertensive postmenopausal women	10 g/day L-citrulline	Yes	4 weeks	NA	4 weeks of L-Citrulline improved muscle oxygenation (higher O_2Hb and TSI, lower HHb) during isometric handgrip exercise. Enhanced oxygen delivery and utilization were observed vs. placebo	NA
7	Wong et al. (2016) [9]	Randomized controlled trial	23 obese postmenopausal women	6 g/day L-citrulline	Yes	8 weeks	Chronic l-citrulline supplementation in obese postmenopausal women resulted in a significant decrease in blood pressure (BP), indicating an improvement in cardiac autonomic function compared to the control group.	NA	8 weeks of L-Citrulline significantly improved cardiac autonomic balance in obese postmenopausal women: ↓ nLF (sympathetic activity), ↑ nHF (vagal tone), ↓ LnLF/LnHF ratio (improved sympathovagal balance), No change in R–R interval (HR remained stable).

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

No	Study	Study Design	Q1	Q2	Q3	Q4	Q5	Overall Appraisal
1	Maharaj et al. (2022)	RCT						5/5 Low Risk of Bias
2	Kang et al. (2023)	RCT						5/5 Low Risk of Bias
3	Maharaj et al. (2022)	RCT						3/5 Moderate Risk of Bias
4	Dillon et al. (2023)	RCT						5/5 Low Risk of Bias
5	Wong et al. (2016)	RCT						3/5 Moderate Risk of Bias
6	Kang et al. (2024)	RCT						4/5 Low Risk of Bias
7	Wong et al. (2016)	RCT						5/5 Low Risk of Bias