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Impact of probiotics and polyphenols on adults with heart failure: a systematic review and meta-analysis

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Abstract

Background Heart failure poses a significant health concern globally, and despite advancements in treatment, the search for additional, supportive therapeutic options remains crucial. This systematic review and meta-analysis studied the impact of probiotics and polyphenols on heart failure biomarkers, focusing on potential improvements in heart function and inflammation.

Methods We analyzed studies published in Embase, PubMed and Cochrane library from 2012 to 2024, focusing on randomized controlled trials. Our findings are drawn from 5 studies on probiotics, involving 401 participants, and 3 studies on polyphenols with a total of 140 participants. The analysis included assessments of LVEF, hs-CRP, creatinine and NT-proBNP levels in intervention and control groups.

Results The probiotics or polyphenols from the included studies did not demonstrate significant changes in the health indicators analyzed for heart failure patients compared to placebo.

Conclusions The systematic review suggested that while the concept of dietary management for heart failure is promising, further research is necessary to validate the efficacy of probiotics and polyphenols as supplementary therapies in heart failure care, by analyzing more diverse health outcomes and patient populations.

Keywords Probiotics, Polyphenols, Heart failure, Meta-analysis

Introduction

Heart failure (HF), a condition where the heart struggles to pump blood effectively, is a significant global health challenge. It affects over 26 million people worldwide, leading to high rates of hospitalization and contributing to a substantial healthcare burden [1, 2]. The mortality rate for young adults aged 15–44 increased from 2.36 in 1999 to 3.16 in 2019, which was a sharper rise than that observed in adults aged 75 and older [3]. Despite advancements in treatments, including medications and devices aimed at improving heart function, the prognosis for many HF patients remains cautious. This underscores the critical need for innovative approaches to complement existing therapies [4]. Exploring dietary strategies, such as probiotics and polyphenols, may provide additional support to improve heart health and address the ongoing challenges faced by these patients.

The exploration of the gut–heart axis, specifically how the gut microbiota interacts with cardiovascular health,

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has opened new avenues for research. An imbalance in gut microbiota, known as dysbiosis, characterized by disruptions in bacterial composition, metabolic activity, or distribution within the gut, has been implicated in the worsening of HF through mechanisms, such as increased systemic inflammation and altered metabolic processes [5–7]. These insights have sparked interest in dietary interventions as potential tools for managing HF. Among these measures, the use of probiotics has shown promise as an effective strategy. They aim to restore a healthy balance of gut microbiota, potentially mitigating some of the pathological processes involved in HF [8]. Some researches have suggested that specific strains of probiotics can have heart-protective effects [9, 10]. For example, *Lactobacillus* and *Bifidobacterium* strains have been associated with reductions in cholesterol levels, improvement in blood pressure control, and a decrease in markers of inflammation [11]. These effects contribute to mitigating the risk factors associated with heart failure. Moreover, probiotics may influence heart health indirectly by improving gut barrier function [12], reducing the absorption of dietary lipids, and modulating immune responses [13].

In addition, polyphenols, which are natural compounds found in plants, are known for their antioxidant and anti-inflammatory properties [14]. These substances can play a beneficial role in heart health by interacting with the body in ways that support cardiovascular well-being [15]. The mechanism through which polyphenols exert their beneficial effects on heart health can be attributed to their ability to remove free radicals [16], thereby reducing oxidative stress, which is a key factor in the development of cardiovascular diseases [17]. Research of Di Pietro and colleagues has shown that polyphenols can influence vascular health by improving endothelial function, enhancing nitric oxide (NO) bioavailability, and inhibiting low-density lipoprotein (LDL) oxidation [18].

Recent studies have highlighted the promising role of probiotics in supporting individuals with heart failure [19], highlighting their ability to improve cardiovascular health [20]. Advancing this line of research, this systematic review and meta-analysis brings in fresh studies and examines the efficacy of probiotics and polyphenols on HF outcomes. By evaluating their impact on clinical characteristics, we aim to assess the viability of these dietary interventions as adjunctive therapies in HF management. The initial objective of this systematic review and meta-analysis was to examine the effects of various dietary interventions, including probiotics, prebiotics, synbiotics, and polyphenols, on heart failure. However, our database search did not find sufficient relevant studies on effect of prebiotics and synbiotics on heart failure. Consequently, we focused on studies involving probiotics and polyphenols. By including these two interventions, we aimed to investigate a wider array of dietary strategies that might benefit heart failure management, despite evaluating them separately. While probiotics and polyphenols are fundamentally different in their mechanisms of action, studying them together in this systematic review and meta-analysis allows for a comprehensive understanding of the potential dietary interventions for heart failure. This approach provides a broader perspective on how different dietary strategies can be used to manage heart failure, acknowledging the multifactorial nature of the disease and the need for diverse therapeutic options.

Materials and methods

Searches of literature and data sources

We conducted the literature search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. Two authors independently searched for relevant studies published between 2012 and 2024 in the Embase, PubMed and Cochrane library databases. We selected this period to capture significant progress in understanding the gut–heart axis, technological advancements in genomic and metabolomic analyses, and shifts toward personalized medicine. The authors applied the PICO model and combined keywords such as (heart failure AND probiotics, heart failure AND polyphenols, etc.) to perform the search, using filters to focus on clinical studies, randomized controlled trials, and articles involving human subjects (Additional file 3: Table S1). We also adhered to the PRISMA checklist to ensure transparency and completeness (Additional file 4: Table S2). After importing the identified articles into EndNote, we removed duplicates and screened abstracts to exclude irrelevant publications based on the inclusion and exclusion criteria. The protocol of this systematic review was registered on PROSPERO with ID CRD42025631407.

Inclusion criteria

We included randomized controlled studies and clinical studies in this systematic review and meta-analysis. The PICO model guided our approach, outlining the following criteria. Population: individuals in the condition of HF or at the risk of HF; intervention: probiotics or polyphenols; comparison: placebo or other probiotics; outcome: the change in left ventricular ejection fraction (LVEF), serum high sensitivity C-reactive protein (hs-CRP), N-terminal pro B-type natriuretic peptide (NT-proBNP), creatinine, Procollagen III, transforming growth factor-β (TGF-β), matrix metallopeptidase 9 (MMP-9), total cholesterol, body mass index (BMI), Tumor Necrosis Factor alpha

(TNF-alpha), Trimethylamine N-oxide (TMAO). Additional inclusion criteria included: (1) sample size of each group ≥ 10 participants; (2) peer-reviewed journal articles; and (3) participants older than 18 years of age.

We excluded studies that contained following: (1) cancer; (2) non-human trials and studies; (3) patients with allergies to probiotics or polyphenols; and (4) non-English publications.

Data extraction

Two reviewers independently selected the full text of the appropriate articles for further consideration and assessment. They resolved disputes through discussion until they reached a mutual understanding. When a mutual understanding could not be reached, a third reviewer stepped in to determine the resolution. The following data was extracted: authors name, year of publication, study design, title, mean age, sample size, probiotic strains and polyphenols type, primary and secondary outcomes. The publications were sorted according to the inclusion and exclusion criteria. During the search there were several articles that met the general criteria but missed some data including outcomes. The authors decided to exclude these studies due to lack of data (Fig. 1).

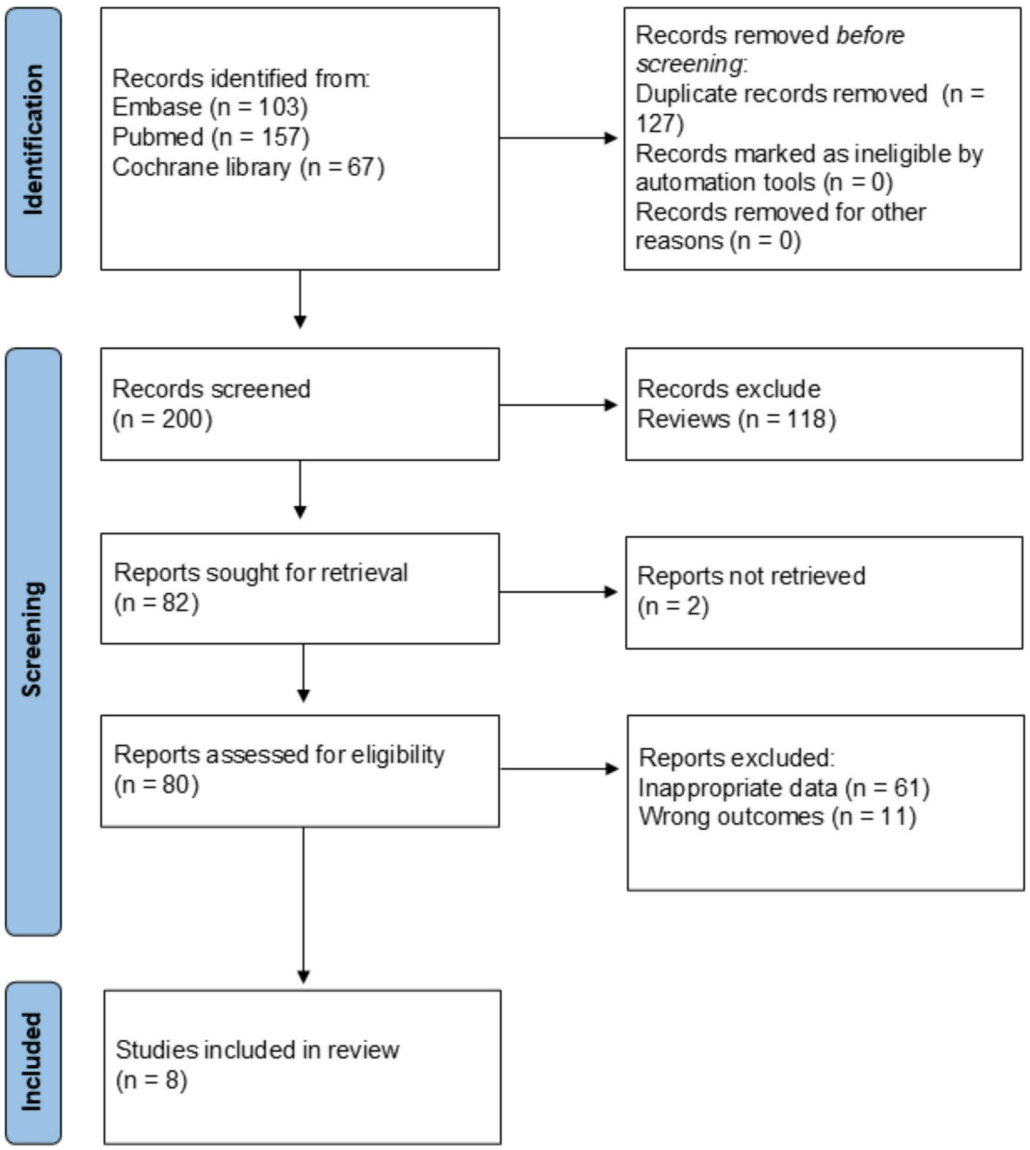

Fig. 1 Flowchart detailing the search methods and findings according to PRISMA guidelines

Quality and bias evaluation

We assessed the bias and methodological quality of the included studies using the Cochrane risk-of-bias tool (RoB 2) [21]. This tool evaluates six specific areas: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias. Two independent reviewers performed the assessment, resolving any disagreements through discussion or by consulting a third reviewer for a final decision. In addition to using the RoB 2 tool to evaluate the quality of the studies, we also considered other potential biases that could affect the results. One important bias is publication bias, where studies with positive results are more likely to be published than those with negative or inconclusive findings. Another bias considered is selection bias, which arises when the participants included in the studies are not fully representative of the wider population. These additional considerations were incorporated to provide a more comprehensive evaluation of potential sources of bias.

Statistical analysis

The study of the effects of probiotics and polyphenols on heart failure metrics adopted a combined approach for data analysis, using Review Manager 5.4.1 software to both analyze the data set and generate forest plots. This analysis incorporated outcomes as continuous variables, utilizing their mean and standard deviation (SD). The statistical method included the Inverse Variance method with a random effects analysis. Both the Study Confidence Interval and the Total Confidence Interval were set at 95%. Mean differences were specifically applied to various health indicators, such as LVEF, hs-CRP, creatinine levels and NT-proBNP.

We also reviewed differences among diverse populations and experimental parameters, including levels of probiotic dosage, participant retention rates, the forms of probiotics and polyphenols used, the study's design, and the length of time each study was conducted (Table 1). The comprehensive impact of probiotics and polyphenols was further investigated through a detailed analysis of subgroups to identify potential sources of variation and to determine whether heterogeneity and moderators affected the outcomes. This detailed analysis was categorized based on participant age, BMI, and levels of NT-proBNP. Age and BMI were included as subgroup variables in the analysis due to their relevance to heart failure and their potential to influence the efficacy of probiotics and polyphenols. Age impacts systemic inflammation, gut microbiota composition, and oxidative stress, which are key factors targeted by these interventions. BMI, as a measure of body composition, is strongly linked to cardiovascular health, gut dysbiosis, and metabolic regulation, all of which can modulate the outcomes of dietary interventions. While age and BMI were used as baseline characteristics, their inclusion as subgroup variables helps explore potential heterogeneity and differences in outcomes based on these factors. NT-proBNP, a biomarker that rises in the blood with the development of heart failure, was selected for subgroup analysis, because it was the only outcome measured in both the probiotics and polyphenols groups. This allowed for a consistent comparison across the studies and provided a clear indication of heart failure progression or improvement in response to the interventions.

Results

Quality and risk of bias assessment

The RoB 2 assessment for individual studies reveals varied risk levels across the assessed domains (Fig. 2). High risk is present in the 'Missing Outcome Data' domain for Karim et al. [22] and Pourrajab et al. [23], indicating significant concerns regarding incomplete data handling. The 'Randomization Process' domain shows unclear risk for Awoyemi et al. [21], Gal et al. [24], Panahi et al. [25], and Pourrajab et al. [23] due to insufficient details on random sequence generation and allocation concealment, potentially introducing selection bias. All studies display low risk in the 'Deviations from Intended Interventions' and 'Measurement of the Outcome' domains, reflecting effective blinding and outcome assessment procedures. Similarly, the 'Selection of the Reported Result' domain indicates low risk across all studies, with comprehensive reporting of prespecified outcomes. Overall, studies such as Costanza et al. [26], Flammer et al. [27], and Moludi et al. [28] demonstrate low overall bias, while Awoyemi et al. [21], Gal et al. [24], and Panahi et al. [25] show unclear risks due to lack of methodological details. Karim et al. [22] and Pourrajab et al. [23] have high overall risk primarily due to the inadequate handling of missing outcome data.

While we conducted a comprehensive search across multiple databases, including Embase, PubMed and Cochrane library, we did not include unpublished studies or gray literature, which could contribute to publication bias (Fig. 3).

The included studies demonstrated variability in participant selection, which may have introduced selection bias. The studies primarily focused on heart failure patients with moderate disease severity (NYHA class II/III) and controlled comorbidities while excluding those with severe conditions (NYHA class IV). Participants with reduced LVEF ($\leq 40\%$) were commonly included, whereas those with preserved or severely reduced LVEF were excluded.

Table 1 Characteristics and aspects of included studies

Authors, year	Study types	Sample size	Mean age (± SD)	Intervention	Dose	Study duration	Measured outcomes	Key results
Awoyemi et al. [21]	Randomized, Phase II, multicenter, randomized, open label, controlled trial	Probiotic: 52 Antibiotic: 48 Control: 51	Probiotic: 62 ± 8 Antibiotic: 59 ± 10 Control: 60 ± 10	Probiotic yeast *S. boulardii*	Intervention: two capsules of 250 mg twice a day Control: Standard of care	12 weeks	LVEF, NT-proBNP, TMAO	No significant effect of LVEF, TMAO, microbiota diversity and CRP
Costanza et al. [26]	Randomized, DB, PC, Parallel design	Probiotic: 10 Placebo: 10	Probiotic: ND Placebo: ND	Probiotic preparation with *S. boulardii*	Intervention: Probiotic (1000 mg/day) for a 3-month daily Control: Placebo for a 3-month daily	3 months	LVEF, hs-CRP, Creatinine, Glycemia, TC, UA	Reduction in total cholesterol, uric acid, and improvmenet in LVEF
Flammer et al. [27]	Randomized, DB, PC	Polyphenol: 10 Placebo: 10	Polyphenol: 60.3 + 10.1 Placebo: 58.1 + 11.9	Flavanol-rich chocolate (FRC)	Intervention: 40 g of FRC Placebo: 28.4 g of control chocolate (CC)	4 weeks	NT-proBNP, hs-CRP, Creatinine	Flow-mediated vasodila-tation significantly improved, platelet adhesion significantly decreased
Gal et al. [24]	DB, PC, single-center design	Polyphenol: 30 Placebo: 30	Polyphenol: 65.8 ± 10.41 Placebo: 67.5 ± 11.50	Resveratrol capsule	Intervention: 100 mg resveratrol capsule daily for 3 months Placebo: Received inactive agent	3 months	LVEF, Hematocrit, WBV, RBC aggregation	No significant effect on hematocrit and viscosity, significant improvement of red blood cell aggregation
Karim et al. [22]	Randomized, DB, PC, multi-site	Probiotic: 53 Placebo: 55	Probiotic: 53 ± 4.9 Placebo: 55 ± 5.6	Vivomixx: 112B capsules containing bifidobacteria, lactobacilli, and *Streptococcus thermophilus*	Intervention: Received Vivomixx 112 billion capsules daily for 12 weeks Control: Received inactive agent	12 weeks	LVEF, hs-CRP, HGS, ASMI, SPPB	Improved HGS, gait speed, and plasma Dkk-1, and reduced plasma zonulin, Dkk-3, and SREBP1
Moludi et al. [28]	Randomized, DB, PC, single center	Probiotic: 22 Placebo: 22	Probiotic: 57.10 ± 7.80 Placebo: 56.70 ± 9.10	*Lactobacillus rhamnosus GG* (LGG) probiotic capsule	Intervention: 1 probiotic capsule (1.6×10^9 CFU) daily; Control: Placebo capsules	3 months	LVEF, hs-CRP, MMP-9, TMAO, Procollagen III	Significant decreases in serum TGF-β, no differences in MMP-9 and procollagen III levels
Panahi et al. [25]	Randomized, DB, PC	Polyphenol: 30 Placebo: 30	Polyphenol: 30 ± 7.9 Placebo: 64.9 ± 9.8	Nanocurcumin	Intervention: 40 mg nanocurcumin capsule twice daily for 7 days Control: placebo dose based on manufacturer's recommendation	7 days	NT-proBNP, Creatinine, IL-6, eGFR	No statistically significant difference in the reduction in IL-6 and NTproBNP levels in the intervention and control groups

Table 1 (continued)

Authors, year	Study types	Sample size	Mean age (± SD)	Intervention	Dose	Study duration	Measured outcomes	Key results
Pourrajab et al. [23]	Randomized, TB, PC, parallel-group trial	Probiotic: 39 Placebo: 39	Probiotic: 53.87 ± 7.25 Placebo: 55.59 ± 8.95	Low-fat probiotic yogurt with *Lactobacillus acidophilus La5* and *Bifidobacterium lactis Bb12*	Intervention: 300 mL of probiotic yogurt/day (3×10^9 cfu per day) Control: 300 mL of regular yogurt/day	10 weeks	NT-proBNP, oxLDL, Pentraxin3	The levels of PTX3 and oxLDL in both the groups decreased significantly ApoB100 significantly decreased in the control group

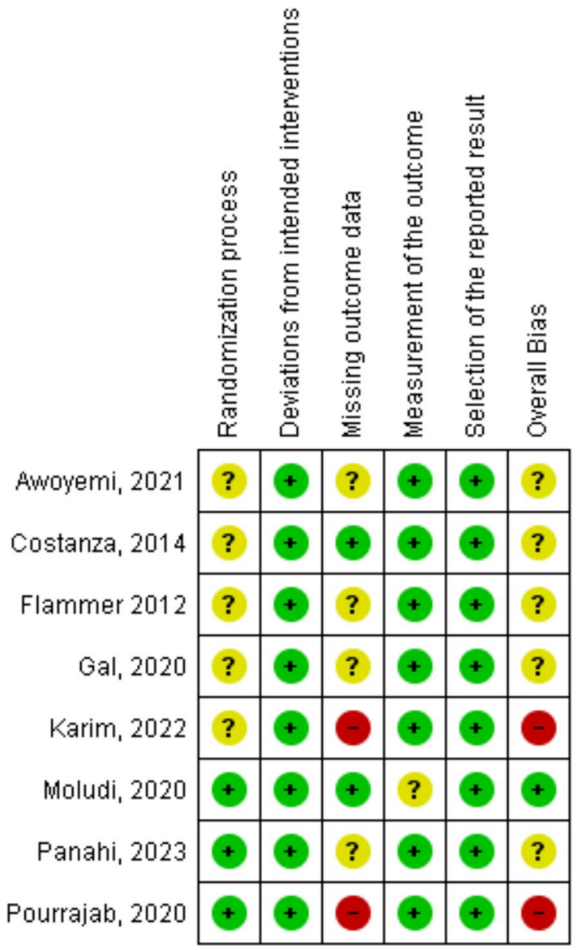

Fig. 2 ROB 2 tool's risk of bias graph for included studies ($n=8$)

Fig. 3 ROB 2 tool's risk of bias summary for included studies ($n=8$)

Effects of intervention on LVEF

Four studies with a combined total of 253 participants investigated the mean difference in LVEF between the probiotics (intervention) and placebo (control) groups. The meta-analysis revealed an overall standard mean difference (SMD) of 0.11 (95% CI −0.19, 0.42) ($p=0.46$), suggesting no statistically significant difference in LVEF between the two groups. Heterogeneity among the studies was moderate ($I^2=27\%$, $p=0.25$). The forest plot representing the effect on LVEF is outlined in Fig. 4a. Individual studies reported SMDs ranging from −0.19 to 0.38, with study weights in the meta-analysis ranging from 7.7 to 37.2%. These results indicate that the intervention did not result in a statistically significant improvement in LVEF compared to the control across the studies included.

Effect of intervention on hs-CRP

Three studies with a combined sample size of 150 individuals assessed the mean difference in hs-CRP levels between the probiotics (intervention) and placebo groups. The analysis indicated that there was no statistically significant difference in the mean hs-CRP levels among patients receiving the intervention, with a total mean difference of −0.13 (95% CI −0.33, 0.08) ($p=0.22$) (Fig. 4b). There was minimal heterogeneity observed across the studies ($I^2=16\%$, $p=0.30$). Analysis of the individual studies within the meta-analysis revealed variations in mean differences of −0.38 mg/dL, −0.30 mg/dL and −0.03 mg/dL; however, none of these were statistically significant. The respective weights of the studies in the meta-analysis were 14.8%, 14.8%, and 70.4%. The results collectively suggest that the intervention did not result in a significant change in hs-CRP levels when compared with the control group across the studies analyzed.

Effect of intervention on creatinine

Two studies with a total of 80 participants were analyzed to assess the mean difference in serum creatinine levels between the polyphenols (intervention) and placebo groups. The meta-analysis revealed an overall mean difference of −3.77 µmol/L (95% CI −23.62, 16.08) ($p=0.71$), indicating no statistically significant difference in serum creatinine levels between the groups. There was no heterogeneity detected between the studies ($I^2=0\%$, $p=0.66$) (Fig. 4c). The individual studies showed mean differences of −5.20 and −9.70 µmol/L, with substantial variation in the treatment effect size, yet neither study achieved statistical significance individually. The weight contribution of the studies to the meta-analysis was 90.4% and 9.6%, respectively. The aggregated data suggests that the intervention does not have a significant impact on serum creatinine levels when compared with the control group.

Effect on NT-proBNP

In the analysis of the impact on NT-proBNP levels, two categories of interventions were examined: probiotics and polyphenols (Fig. 4d). Both subgroups were compared with their respective placebo groups. The probiotics

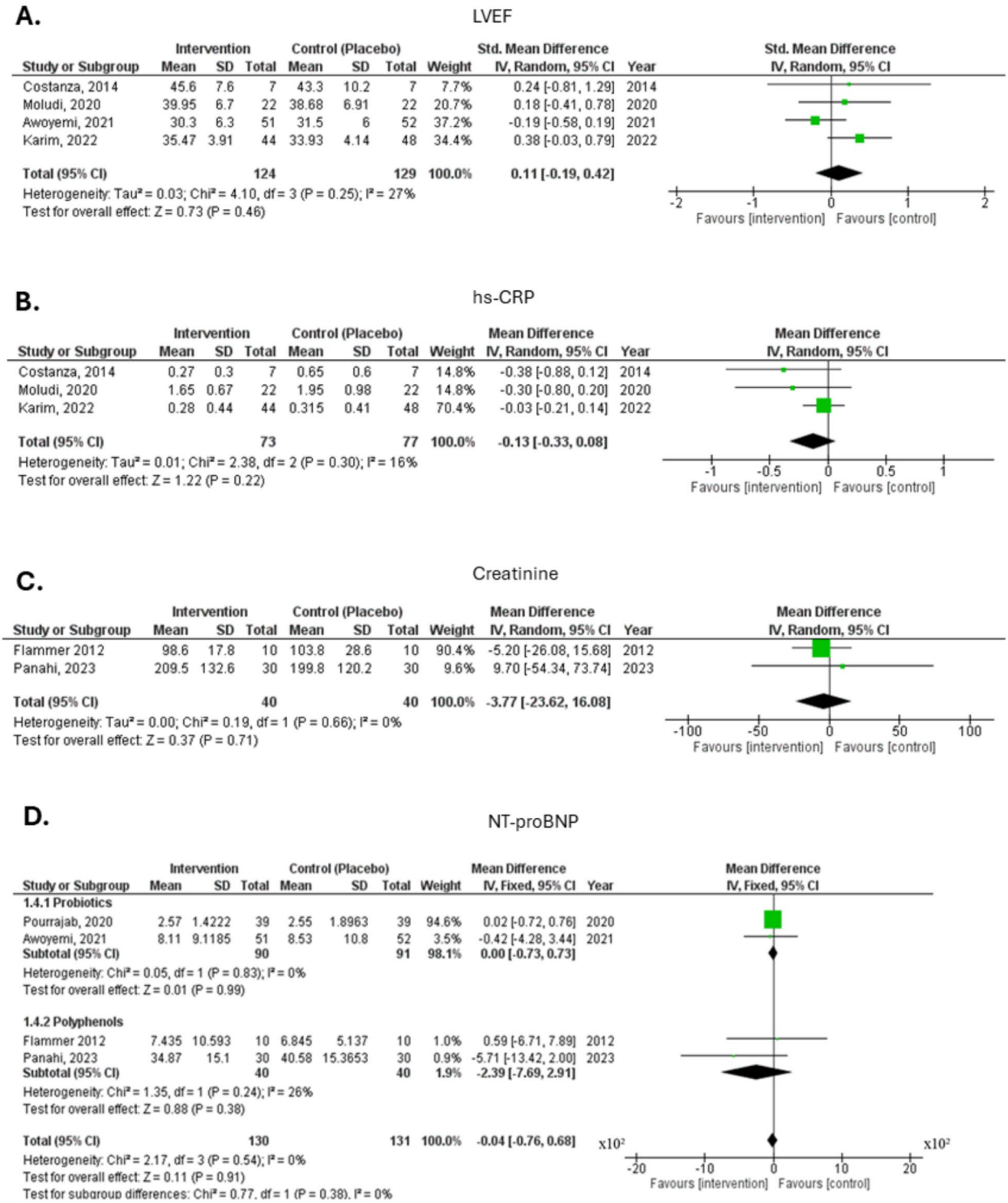

Fig. 4 Forest plots of the effects of intervention on LVEF (**A**), hs-CRP (**B**), creatinine (**C**), NT-proBNP (**D**). ES, effect size; CI, confidence interval

subgroup consisted of two studies with 90 participants and the polyphenols subgroup, also comprising two studies but with 40 participants. The results of analyses of two subgroups were described in the section of "Subgroup analyses." For a clearer visual representation in our forest plot, we employed a scaling technique

Table 2 Analyses of subgroups based on the age, BMI and NT-proBNP

Subgroups	No. of studies	I^2 (%)	Mean difference (95% CI)	*p*
By age				
Probiotics	4	0	2.22 [0.66, 3.77]	0.005
Polyphenols	3	0	−1.55 [−2.53, −0.56]	0.002
By BMI				
Probiotics	2	61	−0.18 [−1.18, 0.83]	0.73
Polyphenols	2	0	−1.07 [−1.63, −0.51]	0.0002
By NT-proBNP				
Probiotics	2	0	0.00 [−0.73, 0.73]	0.99
Polyphenols	2	26	−2.39 [−7.69, 2.91]	0.38

CI, confidence interval

by dividing the original values by 100, subsequently annotating the horizontal axis with "$\times 10^2$", respectively.

When combining both subgroups for an overall effect, the analysis indicated no significant difference in NT-proBNP levels, with an overall mean difference of −0.04 (95% CI −0.76, 0.68) and no detected heterogeneity ($I^2=0\%$, $p=0.91$).

Subgroup analyses of NT-proBNP, age and BMI

In the subgroup analysis of NT-proBNP levels, neither probiotics nor polyphenols showed significant effects. Probiotics, in two studies, resulted in a mean difference of 0.00 (95% CI −0.73, 0.73) with no heterogeneity ($I^2=0\%$, $p=0.99$), and polyphenols, also in two studies, had a mean difference of −2.39 (95% CI −7.69, 2.91) with low to moderate heterogeneity ($I^2=26\%$, $p=0.38$), indicating no significant modifications in NT-proBNP levels. The study weights were 3.5% and 94.6% in the probiotics' subgroup, 1.0% and 9.9% in the polyphenols' subgroup. These analyses suggest that neither probiotics nor polyphenols significantly modify NT-proBNP levels compared to placebo.

Our subgroup analyses examining baseline parameters such as age and BMI across different groups receiving probiotics or polyphenols have revealed significant variances (Table 2). Specifically, within the age subgroup, individuals in the probiotics group demonstrated a favorable baseline mean difference of 2.22 (95% CI 0.66, 3.77) with no heterogeneity ($I^2=0\%$, $p=0.005$), suggesting older individuals are more likely to be in this group compared to the placebo. Conversely, the polyphenols group showed a negative baseline difference in age with a mean of −1.55 (95% CI −2.53, −0.56) with no heterogeneity ($I^2=0\%$, $p=0.002$), indicating a younger demographic compared to their control group (Additional file 1: Fig. S1).

Regarding BMI, the analysis within this subgroup displayed a non-significant difference in the probiotics group, with a mean difference of −0.18 (95% CI −1.18, 0.83) with heterogeneity ($I^2=61\%$, $p=0.73$), indicating a slight trend toward lower BMI but without statistical significance. For the polyphenols group, there was a significant reduction in BMI with a mean difference of −1.07 (95% CI −1.63, −0.51) with no heterogeneity ($I^2=0\%$, $p=0.0002$), suggesting individuals with lower BMI are more prevalent in this group compared to their placebo counterpart (Additional file 2: Fig. S2).

Discussion

Understanding and improving outcomes for heart failure are linked to key physiological and biochemical markers, including LVEF, hs-CRP, creatinine, and NT-proBNP. These biomarkers were the highlights of our analysis, chosen for their universal measurement across the eight included studies and their critical roles in diagnosing, monitoring, and managing heart failure and other cardiovascular diseases [29–31].

The systematic review and meta-analysis conducted on the impact of probiotics and polyphenols on adults with heart failure aimed to uncover the potential benefits of these dietary interventions. Our findings pooling effects from 8 studies with 493 participants, showed no significant improvements in studied heart failure biomarkers. These findings align to some extent with previous meta-analysis, which reported that probiotics did not significantly affect LVEF and hs-CRP levels [19]. This research concentrated on examining how probiotic supplementation might mitigate cardiac remodeling. Similarly, this study investigated comparable outcomes but went further by incorporating the most recent studies into the analysis. In addition, it expanded the scope by also exploring the impacts of polyphenols on heart failure, thereby broadening the understanding of dietary interventions in this context.

The results of this meta-analysis are consistent with those of Clauss et al. [32], where no significant changes in NT-proBNP levels were observed following the consumption of a polyphenol-rich beverage compared to a placebo in marathon runners. This consistency highlights the challenges in determining the effects of dietary interventions, such as polyphenols on heart failure biomarkers, especially NT-proBNP. However, this study presents a contrast to another meta-analysis that reported significant reductions in serum creatinine levels with resveratrol supplementation (WMD = −1.90 μmol/L; 95% CI −3.59 to −0.21; $p=0.03$), suggesting a renal protective effect of this specific type of polyphenol [33]. The contrasting results

between this study and the meta-analysis may originate from several key differences. First, the type of polyphenol investigated plays a crucial role. Resveratrol is known for its unique anti-inflammatory and antioxidant properties [34–36] which may contribute more significantly to renal protection than the broader category of polyphenols analyzed in this study. This specificity could explain the observed efficacy in reducing serum creatinine levels. In addition, the scope of the studies included in the meta-analysis could also influence the outcomes. The resveratrol meta-analysis incorporated a larger number of studies, potentially enhancing the statistical power and sensitivity to detect smaller changes in studied biomarkers. These factors underscore the importance of considering both the chemical diversity of polyphenols and the scale of evidence when interpreting the effects of dietary interventions on health outcomes.

The probiotics studied in the selected articles included strains such as *Lactobacillus rhamnosus GG*, *Saccharomyces boulardii*, and a combination of *Bifidobacterium* and *Lactobacillus* species, found in formulations, such as Vivomixx. These strains have been implicated in various beneficial mechanisms, including reducing systemic inflammation, modulating gut microbiota, and improving metabolic processes that are critically linked with heart failure dynamics.

It was revealed that *Saccharomyces boulardii* significantly lowered the levels of remnant lipoprotein particles and triglyceride-rich lipoproteins, which are related to very low-density lipoprotein. These remnant lipoproteins, resembling LDL, are known to be highly atherogenic and are strongly linked to the severity and advancement of coronary artery disease (CAD), regardless of LDL-C levels. Moreover, elevated remnant lipoprotein levels have been associated with compromised endothelial function in human coronary arteries and serve as significant indicators of cardiovascular events [37]. Comparing the effects of *S. boulardii* on heart failure in two different studies from our meta-analysis, provides a deeper insight into the potential and limitations of using probiotics in cardiovascular health management. The study by Costanza and colleagues demonstrated positive outcomes, where *S. boulardii* supplementation led to significant improvements in LVEF and reductions in certain cardiovascular risk markers such as total cholesterol and uric acid levels in patients with heart failure [26]. Notably, this pilot trial highlighted the potential of *S. boulardii* to modulate cardiovascular health positively, suggesting a beneficial role of this specific yeast in heart failure management.

On the other hand, the randomized trial by Awoyemi and colleagues aimed to examine the effects of *S. boulardii* in a larger, multicentric setup with a more diverse patient population and a rigorous randomized controlled design [21]. Contrary to the initial positive results, this trial found no significant impact of *S. boulardii* on LVEF, microbiota diversity, or systemic inflammation markers CRP and TMAO after 3 months of treatment. This suggests that the effects of *S. boulardii* might not be as robust or consistent across different settings or populations as previously thought. The differences between two trials on *S. boulardii* in heart failure might originate from the pilot study's smaller scale and less controlled design, varying patient demographics with different baseline characteristics and health statuses, and the absence of significant dysbiosis in the Awoyemi and colleagues' trial participants, potentially influencing the probiotic's efficacy. These elements highlight the need for more precise research to determine *S. boulardii's* effectiveness in diverse patient populations.

The subgroup analyses of our meta-analysis, focusing on baseline age and BMI differences among participants receiving probiotics or polyphenols, highlight significant variances that are essential for interpreting the effects of these interventions on heart failure outcomes. Our findings indicate significant differences in age at baseline, with older participants more prevalent in the probiotics group (mean difference of 2.22, $p=0.005$) and younger participants more common in the polyphenols group (mean difference of -1.55, $p=0.002$). These differences are critical to consider as they may affect the generalizability of the intervention effects on heart failure outcomes, given that age can influence disease progression and response to treatments, and age could correlate with different metabolic and physiological states [38, 39]. In terms of BMI, there was a non-significant trend toward lower BMI in the probiotics group (mean difference of -0.18, $p=0.73$) and a significant reduction in the polyphenols group (mean difference of -1.07, $p=0.0002$). This suggests that baseline BMI also varied significantly between groups, which could potentially impact the study outcomes related to heart failure, as BMI is a known factor influencing cardiovascular health [40].

Strengths and limitations

Our systematic review and meta-analysis represent the first comprehensive analysis to evaluate the effects of both probiotics and polyphenols on adults with heart failure. This study demonstrates how various dietary interventions could impact heart failure biomarkers in this patient population. Our methodology, combined with the inclusion of studies up to 2024, makes our findings more relevant and useful for current clinical

practices and dietary advice. This analysis lays an important groundwork for future studies, offering essential insights that will help further explore how these dietary interventions can benefit heart health. One of the primary reasons for the lack of statistical significance in our results may be the limited number of randomized controlled trials available that focus specifically on the impact of probiotics and polyphenols on heart failure, restricting our ability to make generalizable conclusions. Another significant limitation of our review is the variability in probiotic strains, doses, and formulations, as well as the types, doses and sources of polyphenol products evaluated across the included studies. For example, probiotics ranged from *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* to combinations of *Bifidobacterium* and *Lactobacillus* species, with considerable differences in doses and delivery methods, such as capsules or yogurts. Similarly, polyphenols were represented by a broad spectrum of compounds, including resveratrol, flavanols, and nanocurcumin, each with distinct bioactive properties and varying levels of efficacy. This heterogeneity can act as a confounding factor, complicating the ability to isolate specific effects and draw generalized conclusions. In addition, a limitation is the small number of studies investigating specific outcomes, such as NT-proBNP, creatinine, and hs-CRP, making it difficult to draw definitive conclusions about their efficacy. A further limitation of this review is the presence of selection bias, arising from variability in the inclusion and exclusion criteria across the included studies. Most studies focused on specific subgroups of heart failure patients, such as those with moderate disease severity, classified as NYHA class II or III, and controlled comorbidities, while excluding individuals with severe or advanced conditions, such as NYHA class IV. Participants with reduced LVEF, typically 40% or less, were commonly included, whereas those with preserved or severely reduced LVEF were often excluded. This variability may limit the applicability of the findings to broader heart failure populations. Furthermore, the overall small sample sizes and the limited scope of data due to a small number of relevant articles available for inclusion significantly affect the statistical power of our analysis. This limitation is compounded by the variability in the short duration and follow-up periods of the studies, which can influence the long-term applicability and visibility of the effects.

Conclusions

This systematic review and meta-analysis assessed the efficacy of probiotics and polyphenols in managing heart failure. Despite their potential benefits, the results revealed no significant improvements in heart failure biomarkers, such as LVEF, hs-CRP, creatinine, and NT-proBNP. These findings suggest that while dietary interventions remain a promising area for heart failure management, further research with larger and more targeted studies is required to confirm their clinical effectiveness.

Abbreviations

BMI	Body mass index
CI	Confidence interval
HF	Heart failure
hs-CRP	High sensitivity C-reactive protein
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro B-type natriuretic peptide
SD	Standard deviation
SMD	Standard mean difference
TMAO	Trimethylamine N-oxide

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

Author contributions

MN and SK performed the literature review. MN and SK contributed to the conception and design of the study. MN prepared the draft version of the manuscript. MN, SK, ZJ, AN, ShS, ZM and SS analyzed the data. AI, AS, MB, and AK reviewed and edited the manuscript. All the authors approved the final version of the manuscript. The research presented in this paper was conducted by the authors, unless explicitly stated otherwise in the text.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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