Du et al. Reproductive Biology and Endocrinology (2025) 23:146
https://doi.org/10.1186/s12958-025-01466-0

Reproductive Biology and Endocrinology

REVIEW

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Efficacy and safety of nutritional supplements in female infertility: a network meta-analysis

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Abstract

Background Infertility represents a prevalent condition affecting the reproductive system. It has a global incidence of approximately 17.5%. Nutritional supplements are increasingly used as complementary therapy for female infertility, though their efficacy remains controversial. This study aimed to systematically assess the effectiveness of various nutritional supplements in female infertility through a network meta-analysis (NMA).

Methods The Web of Science, Cochrane Library, EMBASE, and PubMed, and databases were retrieved for relevant English articles on the effectiveness of nutritional supplements in female infertility up to April 17, 2025. The quality of articles was assessed via the Cochrane Risk of Bias tool 2.0. The GEMTC package in R software was employed to compare the results via a Bayesian NMA. The mean difference (MD) or risk ratio (RR) and 95% credible interval (CrI) served as effect size indicators. The effectiveness of interventions was evaluated via the surface under the cumulative ranking curve to the total area (SUCRA). The evidence's confidence was evaluated via the confidence in network meta-analysis (CINeMA). $P < 0.05$ indicated statistical significance. Funnel plots were created via Stata 18.0 to assess the publication bias.

Results This NMA included 30 studies with 3,977 patients. The results revealed that compared to alternative interventions, the combination of probiotics and vitamin D exhibited the most significant increase in the clinical pregnancy rate (RR = 1.29, 95% CrI = 1.1, 1.52; CINeMA: Low certainty). Curcumin alone demonstrated a substantial increase in both the number (No.) of oocytes retrieved (MD = 6.96, 95% CrI = 3.23, 10.71; CINeMA: Very low certainty) and the fertilization rate (MD = 9.02, 95% CrI = 2.98, 15.07; CINeMA: Low certainty). Astaxanthin alone resulted in a notable increase in the No. of good-quality embryos (MD = 1.17, 95% CrI = 0.19, 2.16; CINeMA: Very low certainty). Curcumin intake showed the greatest effect on the increase in MII (MD = 6.35, 95% CrI = 3.31, 9.41; CINeMA: Very low certainty). The assessment of adverse events indicated that no interventions were significantly linked to miscarriage.

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Conclusions Nutritional supplements can play a crucial role in regulating the ovarian environment and enhancing pregnancy outcomes for infertile women. The combination of vitamin D with other nutritional supplements, as well as the intake of coenzyme Q10, astaxanthin, or curcumin, was more effective than other nutritional supplements.

Trial registration Its protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251052361.

Keywords Nutritional supplements, Female infertility, Network meta-analysis

Introduction

Infertility is a prevalent disorder of the reproductive system. According to the WHO, infertility is the inability to conceive after 12 months of regular unprotected intercourse [1]. Infertility is classified as primary and secondary [2]. As of 2023, about 17.5% of the global population is affected by infertility [1]. Of these, female infertility accounts for roughly one-third [3]. Infertility is a complex reproductive health problem, affecting individuals physically, psychosocially, and economically. Studies have indicated a link between infertility and mental health concerns, including an elevated risk of psychological disorders such as anxiety and depression. This correlation is also characterized by a decline in self-esteem and an inclination towards social withdrawal [4]. Furthermore, infertility is linked to social stigmatization for traditional fertility culture [5], economic loss for frequent medical visits and stagnant career development [6], and even gender-based physical violence and emotional abuse [7].

Female infertility is most commonly attributed to ovulatory dysfunction, accounting for 25% of all cases [8]. Of these cases, more than 80% are attributed to polycystic ovary syndrome (PCOS) [9]. The treatment options are determined by the specific diagnosis and may include medically assisted reproduction (MAR) and surgery [10]. Of these, surgery is more restrictive due to its invasive nature. MAR encompasses a range of fertility treatments, including ovulation-promoting drugs, assisted fertilization techniques, and in-vitro fertilization (IVF). These procedures are often accompanied by high costs and a low success rate of only about 29% [11]. Additionally, MAR is frequently associated with extensive sex hormone interventions, which may further impact the health of infertile woman [12]. Given these limitations, many patients undergoing MAR seek complementary therapies, particularly nutritional supplements, to improve treatment success and health status [13].

Accumulating evidence supports the significance of nutritional supplements, including amino acids, coenzyme Q10, melatonin, inositol, and vitamins, in female infertility [13]. Studies have demonstrated that more than 50% of infertile women in the European and Oceania regions take nutritional supplements while undergoing MAR [14–16]. Although most studies indicate that nutritional supplements are safe for women of childbearing age, there remains a lack of clinical guidance on their efficacy and use in female infertility.

Existing guidelines [17] on the use of nutritional supplements in infertile women are limited to the use of folic acid (FA) for the prevention of neurological deficiencies rather than for assisted conception [18]. Furthermore, existing reviews have focused on the efficacy of a single nutritional supplement in infertile women [19]. Few studies have compared the efficacy of different nutritional supplements. Given the wide range of nutritional supplements, this study employed a systematic review and network meta-analysis (NMA) to compare the effects of various nutritional supplements on female infertility, combining both direct and indirect evidence from previous research. This may inform evidence-based recommendations for complementary therapies and guide public health policies and clinical guidelines.

Methods

This NMA adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [20]. Its protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251052361.

Article retrieval

The Web of Science, Cochrane Library, Embase, and PubMed databases were retrieved from the creation of each database up to April 17, 2025. Only English-language articles were included. The retrieval combined subject terms and free words, including 'Infertility, Female'; 'Female Sterility'; 'Nutrition supplement'; 'Dietary Supplements'; 'Coenzymes'; 'Vitamins'; 'Inositol'; 'Arginine'; 'Minerals'; 'Antioxidants'; 'Melatonin'. To ensure a complete search, references in other relevant articles as well as gray literature were manually retrieved. The search strategy is detailed in Table S1.

Eligibility criteria

The following criteria were employed to include articles: (a) Study population: infertile women; (b) Intervention: nutritional supplements, Control: placebo or conventional treatment; (c) Study type: randomized controlled trial (RCT); (d) Outcome indicators: clinical pregnancy rate (CPR), miscarriage rate (MR), fertilization rate (FR), No. of good-quality embryos (NGE), number (No.) of oocytes retrieved (NOR), No. of follicle at Metaphase II (MII).

The following criteria were adopted to exclude articles: (a) Cellular or animal experiments, case reports, scientific experiment plans, reviews, letters, editorials, conference papers, etc.; (b) Articles with missing or grossly erroneous study data; (c) Duplicate publications; (d) Full text not available; and (e) Articles with duplicate participants.

Data extraction

Articles from the retrieval were imported into EndNote. Two independent researchers (C.L. and H.Z.) screened eligible studies by reading the titles and abstracts first and then the full texts. Any disagreements were settled following a discussion or after seeking advice from a third researcher (Z.S.). Data were extracted individually by two researchers (R.J. and Q.L.) via a pre-defined spreadsheet, including the first author, publication year, intervention and control, country, duration of the course, outcome indicators, and basic information about study population.

Quality assessment

Two researchers (X.Z. and J.L.) independently assessed the quality of eligible articles via the Cochrane Risk of Bias tool (RoB 2.0) [21]. The RoB2.0 criteria consist of five aspects: selective reporting, missing data, blinding, allocation concealment, and generation of randomized sequences. Each aspect was rated as 'low risk', 'some concerns', or 'high risk'. The overall quality of articles is determined as follows. If all five aspects are classified as low risk or only one aspect is medium risk and the rest aspects are low risk, the article is classified as a low-risk study. If four or more aspects are classified as medium risk or any one aspect is high risk, the article is designated as a high-risk study. In the remaining cases, the article is classified as a medium-risk study. Two researchers (J.D. and Q.L.) completed the quality assessment independently. Any discrepancies were reviewed by a third researcher (H.Z.).

Statistical analysis

Outcome indicators included dichotomous and continuous variables. The mean difference (MD) or risk ratio (RR) and 95% credible interval (CrI) served as effect size indicators. This study utilized a Markov Chain Monte Carlo approach to develop a Bayesian NMA model [22]. The model was adopted for estimating the relative efficacy of different treatment options. The test process was performed with a model chain value of 4, an annealing value of 10,000, an iteration value of 50,000, a step size of 10 for each test, and an initial value of 2.5. The aim of the process was to derive the posterior distribution [23]. The execution of an NMA requires the fulfillment of three basic assumptions: consistency, homogeneity, and transferability assumptions. Heterogeneity was analyzed via the mtc: anohe function in the GeMTC package. When the overall I^2 was $<50\%$, the homogeneity assumption was satisfied, and the heterogeneity of included studies between the same comparisons was acceptable [23]. Inconsistency between indirect and direct comparisons was tested via the node splitting method, and the mtc. nodesplit function in the GeMTC package was utilized. When $p>0.05$, it indicated no inconsistency between direct and indirect comparisons, and the consistency assumption was satisfied [24]. The convergence of results was determined by calculating the potential scale reduction factor (PSRF), with 1 as the criterion. $1 \le \text{PSRF} < 1.05$ was deemed successful convergence. A network structure was developed using the relationship between the standardized MDs between interventions as the line and each intervention as a node. One node represents an intervention, and a line indicates a direct comparison between interventions. Cumulative probability ranking plots were analyzed. All cumulative ranking probabilities were estimated and reported as the surface under the cumulative ranking curve (SUCRA), i.e., cumulative probability ranking. Sensitivity analysis was performed using a stepwise elimination method for studies with a high risk of bias. Funnel plots were utilized to assess potential publication bias. STATA (version 15.1) and R (version 4.4.1) software were adopted for all statistical analyses.

Certainty assessment

The CINeMA (confidence in NMA) tool (available at http://cinema.ispm.ch) was applied to assess the evidence's quality for all pairwise comparisons. CINeMA tool is a methodological framework for evaluating the reliability of NMA results [25]. This framework encompasses six key areas: within-study bias (RoB), between-study bias (publication or reporting bias), inconsistency, heterogeneity, imprecision, and indirectness. Each area can be categorized into three groups according to the degree of bias: no concern (no downgrade), some concern (downgrade by one level), and serious concern (downgrade by two levels). The evidence from pairwise comparison was ultimately classified as 'very low', 'low', 'medium', or 'high'.

Results

Article retrieval and screening

The retrieval yielded 6,605 articles. After excluding 1,002 duplicates, 5,522 were removed according to the titles and abstracts. The rest were thoroughly reviewed in accordance with the eligibility criteria. Finally, 30 articles were included in the NMA. The screening process is detailed in Fig. 1.

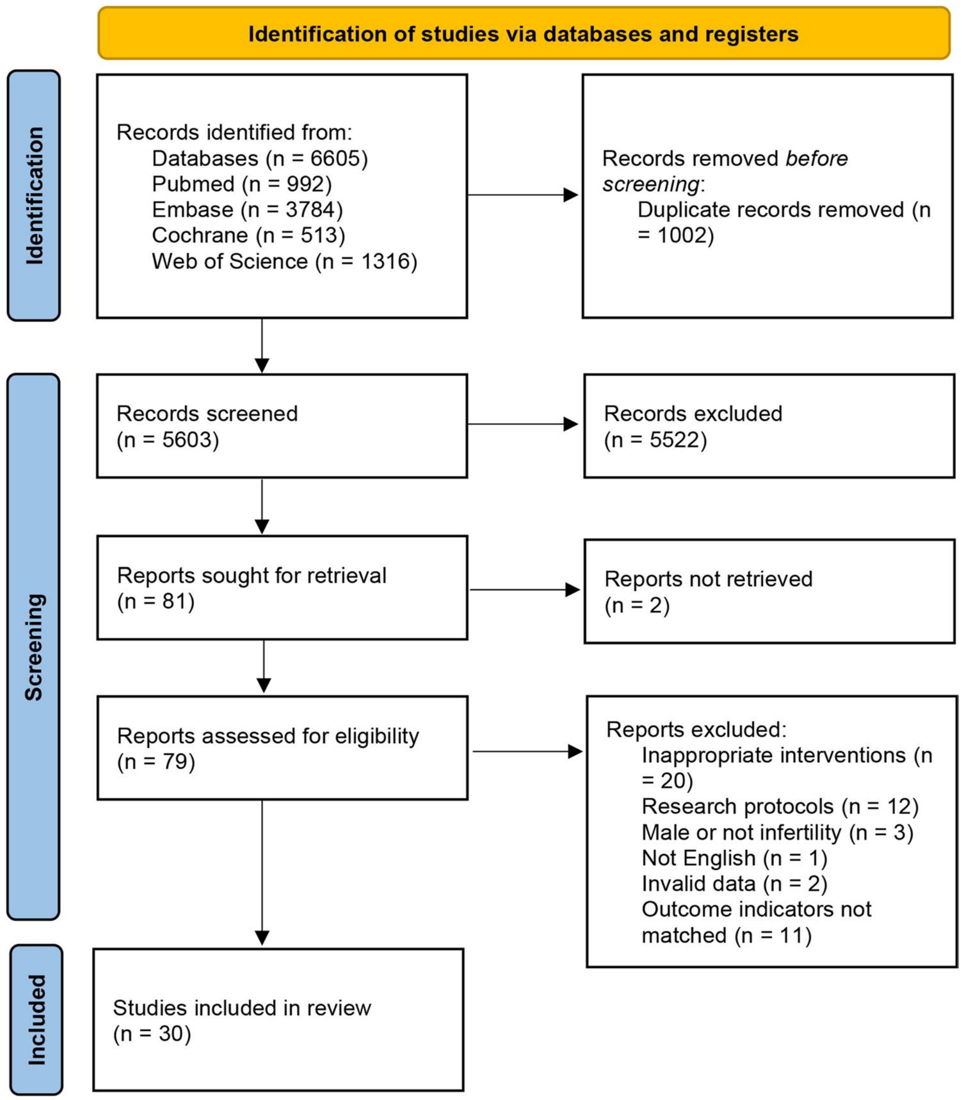


Fig. 1 Flowchart for literature search and screening

Basic characteristics and quality assessment of included studies

This NMA encompassed 30 studies [26–55] from 11 countries (Iran, Italy, Turkey, Australia, China, Austria, Germany, India, Iraq, Spain, Bangladesh), involving 3,977 infertile women with an age distribution of 23–40 years. Nineteen interventions were involved. The single intervention included placebo, routine treatment, L-arginine, astaxanthin, resveratrol, folic acid (FA), melatonin, vitamin D, vitamin C, curcumin, coenzyme Q11, probiotic, and selenium (Se), as well as mononucleotide. Combined interventions included Myo-inositol + FA, Myo-inositol + FA + melatonin, melatonin + Myo-inositol + FA + Se, vitamin D + vitamin E, and probiotic + vitamin D. Relevant information is illustrated in Table 1.

The RoB assessment results are presented in Fig. 2. Among them, 18 studies showed low risk, indicating high methodological quality. A total of 11 studies were found to be at moderate risk in the blinding assessment, and one study was found to be at high risk in the randomization assessment. 23 studies were evaluated as moderate risk because they did not use intention-to-treat (ITT) analysis. In the overall bias risk assessment, eleven studies were classified as medium risk for the absence of a blinding method or a loss rate exceeding 10%. One study was designated as high risk for its unscientific grouping method. After conducting a sensitivity analysis on high-risk studies, the results did not change significantly, indicating that the NMA model is stable.

NMA results

Network relationship diagram

In the network relationship diagram, each dot represents an intervention, and the dot's size is positively

Table 1 Basic characteristics of included studies

Authors	Year	Study Design	Study Country	Interventions	Sample Size	Ages	Treatment Duration	Infertility Type	Outcomes
C. Battaglia et al.	2002	RCT	Italy	Larginine	16	33.8 ± 3.1	8 D	Unexplained	Fertilization rate, MII, No. of retrieved oocytes
				Placebo	16		8 D		
Z. Yazdanpanah et al.	2025	RCT	Iran	Myo inositol + Folic acid	30	27.77 ± 3.3	6 W	Unexplained	MII, No. of retrieved oocytes, No. of good quality embryos
				Folic acid	30	28.43 ± 3.07	6 W		
G. Griesinger et al.	2002	RCT	Austria	Vitamin C	461	31.7 ± 4.4	14 D	Unexplained	Clinical Pregnancies rate
				Placebo	158		14 D		
S. Rostami et al.	2023	RCT	Iran	Astaxanthin	25	33.33 ± 4.97	12 W	Endometriosis	Clinical Pregnancies rate, Fertilization rate, MII, No. of retrieved oocytes, No. of good quality embryos
				Placebo	25	32.08 ± 5.09	12 W		
F. Fereidouni et al.	2024	RCT	Iran	Astaxanthin	22	29.86 ± 4.27	12 D	Polycystic ovary syndrome	Fertilization rate, MII
				Placebo	22	31.14 ± 6.21	12 D		
S. Gerli et al.	2022	RCT	Italy	Resveratrol	40	36.10 ± 0.60	12 W	Unexplained	Clinical Pregnancies rate, Fertilization rate, MII, No. of retrieved oocytes, Miscarriage rate
				Folic acid	50	36.60 ± 0.60	12 W		
L. Doryanizadeh et al.	2021	RCT	Iran	Calcitriol	36	32.50 ± 4.90	4 W	Unexplained	Clinical Pregnancies rate, Miscarriage rate
				Placebo	38	31.60 ± 4.90	4 W		
J. M. J. Tunon et al.	2017	RCT	Spain	Melatonin + Myo inositol + Folic Acid + Selenium	60	34.88 ± 4.69	2 M	Unexplained	Clinical Pregnancies rate, MII, Miscarriage rate
				Placebo	60	34.32 ± 5.85	2 M		
F. S. Hosseini et al.	2021	RCT	Iran	Melatonin	35	32.62 ± 4.80	3 W	Tubal factor or unexplained	Clinical Pregnancies rate, MII, No. of retrieved oocytes, No. of good quality embryos
				Routine treatment	42	32.07 ± 4.90	3 W		
P. Rizzo et al.	2010	RCT	Italy	Myo inositol + Folic acid + Melatonin	32	37.81 ± 2.61	4 W	Unexplained	Clinical Pregnancies rate, Fertilization rate, MII, Miscarriage rate
				Myo inositol + Folic acid	33	38.09 ± 1.97	4 W		
A. Aflatoonian et al.	2014	RCT	Iran	Vitamin D	51	28.45 ± 3.74	4 W	Unexplained	Clinical Pregnancies rate
				Placebo	55	29.56 ± 4.68	4 W		
E. Badihi et al.	2025	RCT	Iran	Probiotic	28	25.6 ± 3.52	2 M	Unexplained	Clinical Pregnancies rate
				Vitamin D	28	22.55 ± 2.72	2 M		
				Probiotic + Vitamin D	28	23.50 ± 3.82	2 M		
				Routine treatment	28	24.21 ± 4.82	2 M		
S. Abedi et al.	2019	RCT	Iran	Vitamin D	42	31.9 ± 4.20	3 M	Unexplained	Clinical Pregnancies rate
				Placebo	43	30.8 ± 4.40	3 M		
S. Zadeh Modarres et al.	2022	RCT	Iran	Selenium	20	32.6 ± 4.60	8 W	Polycystic ovary syndrome	Clinical Pregnancies rate
				Placebo	20	32.8 ± 4.10	8 W		
X. Lu et al.	2018	RCT	China	Vitamin C	137	31.5 ± 3.50	8 W	Unexplained	Clinical Pregnancies rate, No. of retrieved oocytes
				Routine treatment	132	32.1 ± 3.10	8 W		
I. A. Fahad et al.	2020	RCT	Iraq	Vitamin D	43	28.88 ± 7.59	8–12 W	Unexplained	Clinical Pregnancies rate
				Placebo	43	29.27 ± 7.49	8–12 W		
R. D. Gohadkar et al.	2024	RCT	India	Mononucleotide	50	34.1 ± 2.66	3 M	Polycystic ovary syndrome	Clinical Pregnancies rate
				Placebo	50	33.15 ± 3.07	3 M		
G. F. Brusco et al.	2013	RCT	Italy	Folic acid + Inositol	58	/	3 M	Polycystic ovary syndrome	Clinical Pregnancies rate, No. of retrieved oocytes
				Folic acid	91	/	3 M		
S. Akter et al.	2023	RCT	Bangladesh	Melatonin	40	25.20 ± 3.58	8 W	Polycystic ovary syndrome	Clinical Pregnancies rate
				Routine treatment	34	25.18 ± 3.45	8 W		
S. Fernando et al.	2018	RCT	Australia	Melatonin	120	35.4 (4.2)	4 W	Unexplained	Clinical Pregnancies rate, No. of retrieved oocytes, No. of good quality embryos
				Placebo	40	35.2 (4.2)	4 W		
Ö. Emekçi Özay et al.	2017	RCT	Turkey	Myo inositol + Folic acid	98	28.65 ± 3.13	12 W	Polycystic ovary syndrome	Clinical Pregnancies rate, Miscarriage rate
				Folic acid	98	28.81 ± 4.21	12 W		

Table 1 (continued)

Authors	Year	Study Design	Study Country	Interventions	Sample Size	Ages	Treatment Duration	Infertility Type	Outcomes
F. Seyedoshohadaei et al.	2022	RCT	Iran	Myo inositol + Folic acid	30	35.67 ± 5.20	12 W	Unexplained	Clinical Pregnancies rate, MII, No. of retrieved oocytes, No. of good quality embryos, Miscarriage rate
				Folic acid	30	32.90 ± 4.65	12 W		
A. Akbari Sene et al.	2019	RCT	Iran	Myo inositol + Folic acid	25	31.3 ± 4.1	4 W	Polycystic ovary syndrome	Fertilization rate, No. of retrieved oocytes
				Folic acid	25	29.78 ± 4.5	4 W		
R. Jannatifar et al.	2025	RCT	Iran	Curcumin	25	32.6 ± 3.8	10 W	Endometriosis	Clinical Pregnancies rate, MII, No. of retrieved oocytes, Fertilization rate
				Placebo	25	31.1 ± 3.3	10 W		
Y. Xu et al.	2018	RCT	China	Coenzyme Q11	76	32.50 ± 3.30	60 D	Poor ovarian response	Clinical Pregnancies rate, No. of retrieved oocytes, Fertilization rate, Miscarriage rate
				Placebo	93	31.92 ± 3.68	60 D		
B. Lesoine et al.	2016	RCT	Germany	Myo inositol + Folic acid	15	/	8 W	Polycystic ovary syndrome	Fertilization rate, MII, No. of retrieved oocytes
				Placebo	14	/	8 W		
Z. I. Bhatti et al.	2019	RCT	Australia	Vitamin D	42	28.95 ± 4.4	6 W	Unexplained	Clinical Pregnancies rate
				Placebo	40	29.06 ± 3.6	6 W		
F. Fatemi et al.	2017	RCT	Iran	Vitamin D + Vitamin E	52	28.07 ± 4.21	8 W	Polycystic ovary syndrome	Clinical Pregnancies rate, No. of retrieved oocytes, Fertilization rate
				Placebo	53	28.13 ± 3.73	8 W		
E. Somigliana et al.	2021	RCT	Italy	Vitamin D	308	34.65 ± 3.72	2–12 W	Unexplained	Clinical Pregnancies rate, No. of retrieved oocytes, Fertilization rate, Miscarriage rate
				Placebo	322	35.00 ± 2.97	2–12 W		
M. Asadi et al.	2014	RCT	Iran	Vitamin D	55	26.29 ± 3.80	8 W	Polycystic ovary syndrome	Clinical Pregnancies rate
				Placebo	55	26.09 ± 3.46	8 W		

linked to the number of studies involved in each intervention. Larger dots indicate a greater number of studies included. A line between two dots indicates a direct comparative study between these two interventions, and its thickness represents the number of studies between the two interventions. A thicker line indicates a greater number of relevant comparative studies, as shown in Figs. 3 and 4. The PRSF for all results was 1, indicating successful convergence of the model (Figures S1-S6). The node splitting method was adopted for analyzing each closed-loop outcome (Fig. 3A). The results demonstrated no local inconsistency since all *p*-values were more than 0.05 in the outcome indicators (Figure S7). The quality assessment results of evidence (CINeMA) are presented in Table S2.

Primary outcomes

Clinical pregnancy rate

Twenty-six studies reported CPR. The heterogeneity analysis demonstrated an I^2 of 14%, indicating low overall heterogeneity, and the fixed-effects model (FEM) was adopted. This NMA indicated that CPR was substantially higher in infertile women after supplementation with vitamin D (CINeMA: Low certainty), vitamin D + vitamin E (CINeMA: Moderate certainty), coenzyme Q10 (CINeMA: Low certainty), probiotic + vitamin D (CINeMA: Low certainty), mononucleotide (CINeMA: Low certainty) compared to placebo (vitamin D vs. placebo: RR = 1.29, 95% CrI = 1.1, 1.52; vitamin D + vitamin E vs. placebo: RR = 2.76, 95% CrI = 1.67, 5.07; coenzyme Q10 vs. placebo: RR = 1.84, 95% CrI = 1.06, 3.31; probiotic + vitamin D vs. placebo: RR = 2.9, 95% CrI = 1.45, 6.48; mononucleotide vs. placebo: RR = 2.09, 95% CrI = 1.35, 3.43), as detailed in Table 2.

The SUCRA probability ranking revealed the following results: probiotic + vitamin D (90.65%) > vitamin D + vitamin E (90.08%) > Myo-inositol + FA + melatonin (80.26%). Notably, the intake of probiotic + vitamin D was the most effective for improving CPR, as illustrated in Fig. 5A.

No. of oocytes retrieved

Nineteen studies reported NOR. The heterogeneity analysis demonstrated an I^2 of 12%, indicating low overall heterogeneity, and the FEM was used. This NMA indicated that NOR was substantially higher in infertile women after supplementation with astaxanthin (CINeMA: Very low certainty), curcumin (CINeMA: Very low certainty), coenzyme Q11 (CINeMA: Very low certainty) compared to placebo (astaxanthin vs. placebo: MD = 4.12, 95% CrI = 1.78, 6.46; curcumin vs. placebo: MD = 6.96, 95% CrI = 3.23, 10.71; coenzyme Q11 vs. placebo: MD = 1.29, 95% CrI = 0.6, 1.98), as detailed in Table 3.

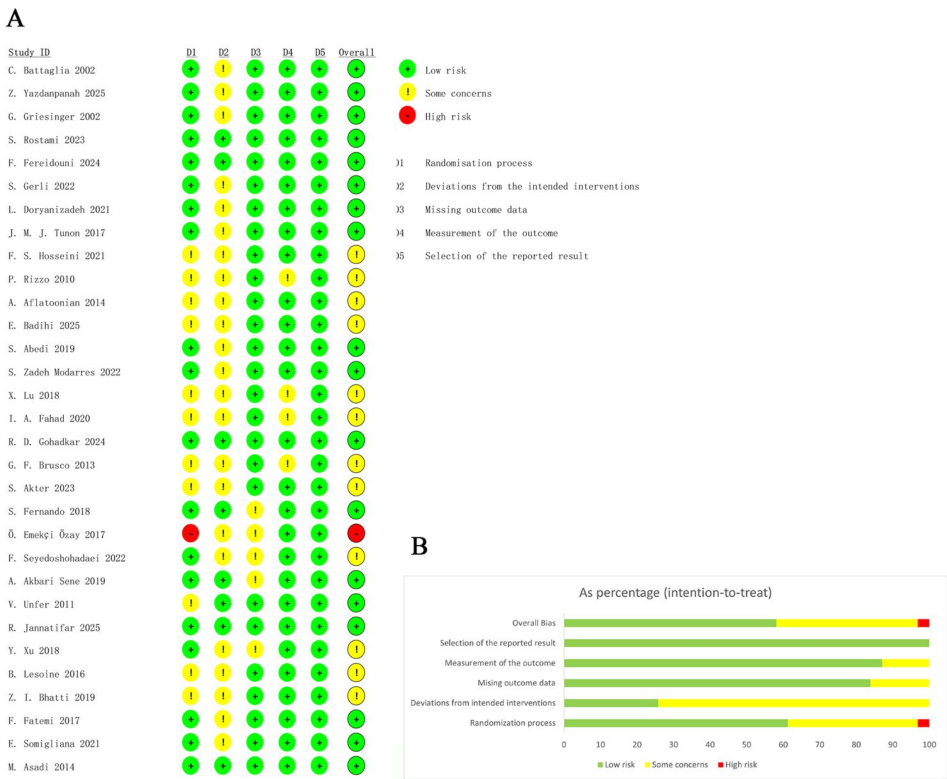


Fig. 2 Figures of risk of bias assessment of included studies by RoB v2.0 tool (**A**) Domain, and overall risk of bias; (**B**) Weighted bars plot of risk of bias evaluation of included studies

The SUCRA probability ranking demonstrated the following results: curcumin (99.11%) > Astaxanthin (92.60%) > Coenzyme Q11 (75.66%). Notably, the intake of curcumin most effectively improved NOR, as illustrated in Fig. 5B.

Secondary outcomes

Fertilization rate

Eleven studies reported FR. The heterogeneity analysis demonstrated an I^2 of 1%, indicating low overall heterogeneity, and the FEM was adopted. This NMA indicated that FR was substantially higher in infertile women after supplementation with curcumin (CINeMA: Low certainty) compared to placebo (curcumin vs. placebo: MD = 9.02, 95% CrI = 2.98, 15.07), as illustrated in Table 4.

The SUCRA probability ranking revealed the following results: Myo-inositol + FA + melatonin (74.39%) > curcumin (71.83%) > Myo-inositol + FA (67.21%). Notably, the intake of Myo-inositol + FA + melatonin was the most effective in improving FR, as illustrated in Fig. 6A. However, given that the NMA results only showed a significant effect of curcumin on FR, the interpretation of Myo-inositol + FA + melatonin should be considered with caution.

No. of good-quality embryos

Ten studies reported NGE. The heterogeneity analysis demonstrated an I^2 of 14%, indicating low overall heterogeneity, and the FEM was adopted. This NMA indicated that NGE was substantially higher in infertile women after supplementation with astaxanthin (CINeMA: Very low certainty), melatonin + Myo-inositol + FA + Se (CINeMA: Very low certainty), and Myo-inositol + FA + melatonin (CINeMA: Very low certainty) compared to placebo (astaxanthin vs. placebo: MD = 1.17, 95% CrI = 0.19, 2.16; melatonin + Myo-inositol + FA + Se vs. placebo: MD = 0.27, 95% CrI = 0.05, 0.49; Myo-inositol + FA + Melatonin vs. placebo: MD = 0.64, 95% CrI = 0.17, 1.1), as illustrated in Table 5.

The SUCRA probability ranking revealed the following results: astaxanthin (92.58%) > Myo-inositol + FA + melatonin (78.66%) > melatonin + Myo-inositol + FA + Se (60.72%). Notably, the intake of astaxanthin most effectively improved NGE, as illustrated in Fig. 6B.

MII

Ten studies reported MII. The heterogeneity analysis demonstrated an I^2 of 34%, indicating low overall heterogeneity, and the FEM was adopted. This NMA indicated

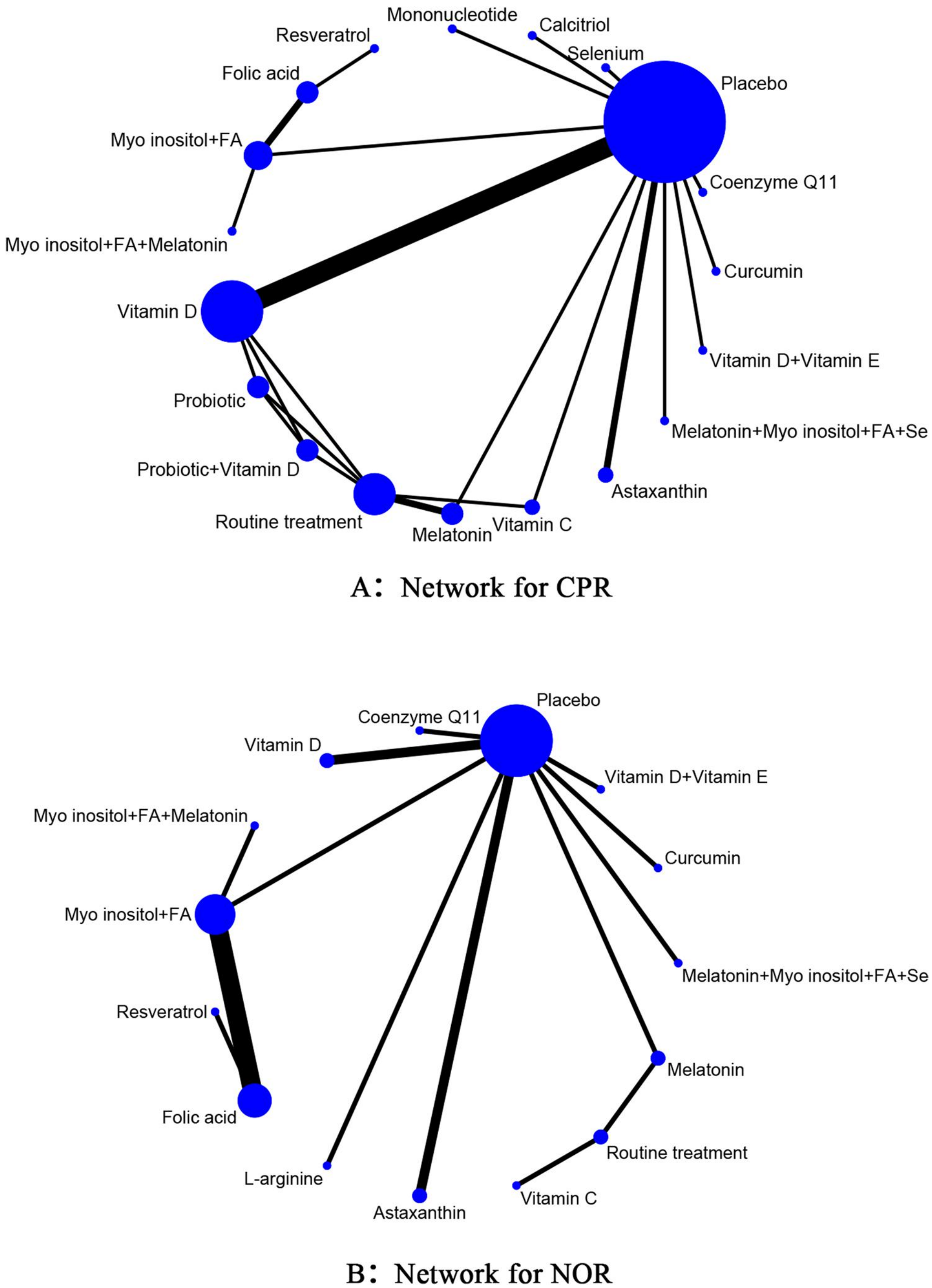


Fig. 3 Network plot. **A**: Clinical Pregnancy Rate (CPR), **B**: No. of oocytes retrieved (NOR)

that MII was substantially higher in infertile women after supplementation with astaxanthin (CINeMA: Very low certainty), resveratrol (CINeMA: Very low certainty), and curcumin (CINeMA: Very low certainty) compared to placebo (astaxanthin vs. placebo: MD = 3.3, 95% CrI = 1.56, 5.05; resveratrol vs. placebo: MD = 0.78, 95% CrI = 0.24, 1.32; curcumin vs. placebo: MD = 6.35, 95% CrI = 3.31, 9.41), as depicted in Table 6.

The SUCRA probability ranking revealed the following results: curcumin (99.44%) > astaxanthin (87.91%) > resveratrol (71.92%). Notably, the intake of curcumin was the most efficacious for ameliorating MII, as illustrated in Fig. 6C.

Adverse events (AEs)

Miscarriage rate (MR)

Eight studies reported MR. The heterogeneity analysis demonstrated an I^2 of 26%, indicating low overall heterogeneity, and the FEM was adopted. This NMA indicated that MR exhibited no significant change in infertile

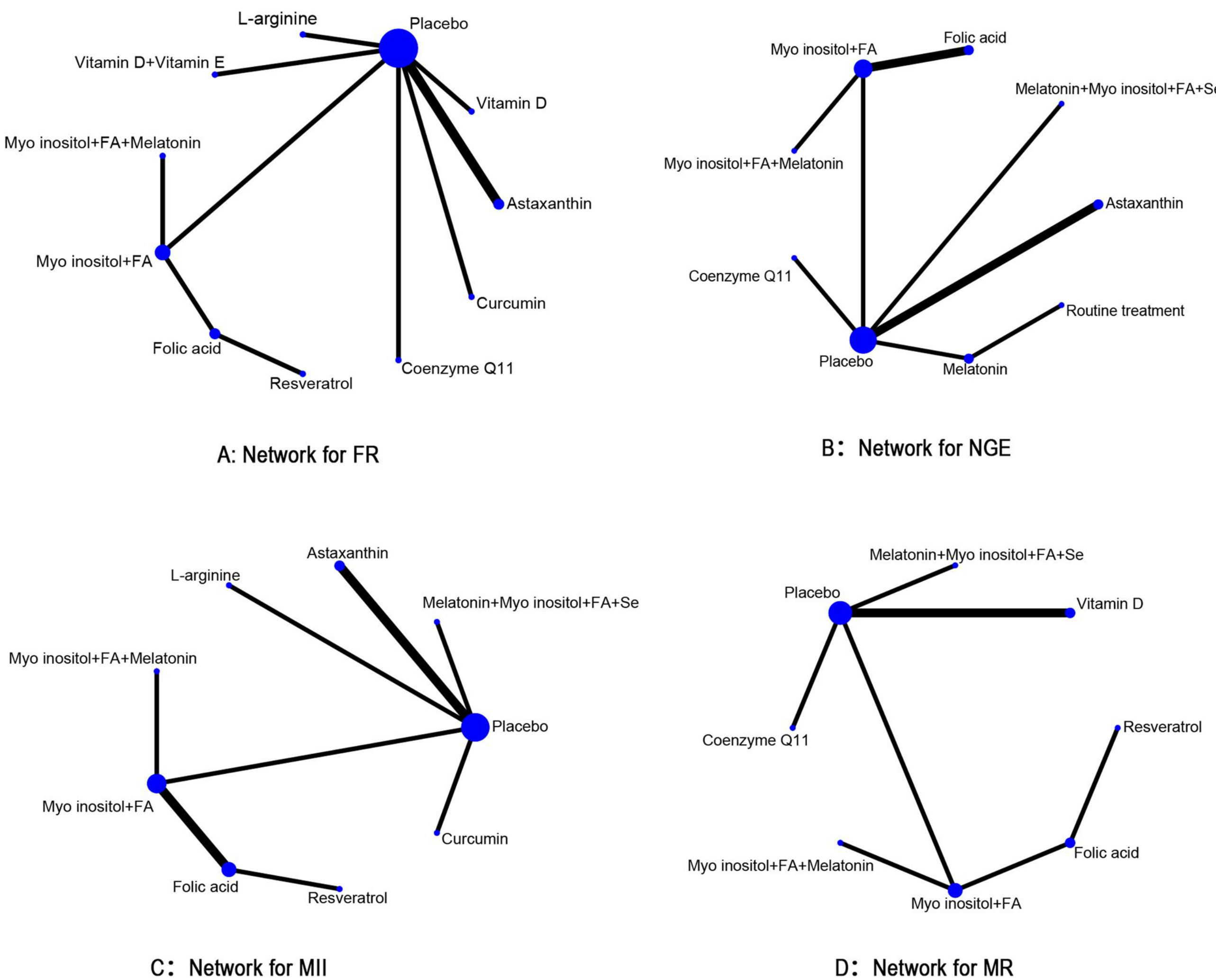


Fig. 4 Network plot. **A**: Fertilization rate (FR), **B**: No. of good-quality embryos (NGE), **C**: MII, **D**: Miscarriage rate (MR)

women after the use of nutritional supplements compared to placebo, as illustrated in Table 7.

The SUCRA probability ranking revealed the following results: melatonin + Myo-inositol + FA + Se (67.93%) > Myo-inositol + FA (60.05%) > placebo (58.90%). The risk of miscarriage was highest after the intake of melatonin + Myo-inositol + FA + Se, as shown in Fig. 6D. The ranked results of SUCRA need to be interpreted with caution as no significant correlation was observed.

Publication bias

Funnel plots were created to evaluate publication bias. The results revealed that all plots were symmetric, suggesting no publication bias (Figs. 7 and 8).

Meta-regression

Meta-regressions (sample size, course of treatment, publication year) were adopted for each outcome to explore possible sources of heterogeneity and the stability of results. No significant results were seen in all regression analyses, suggesting stable results.

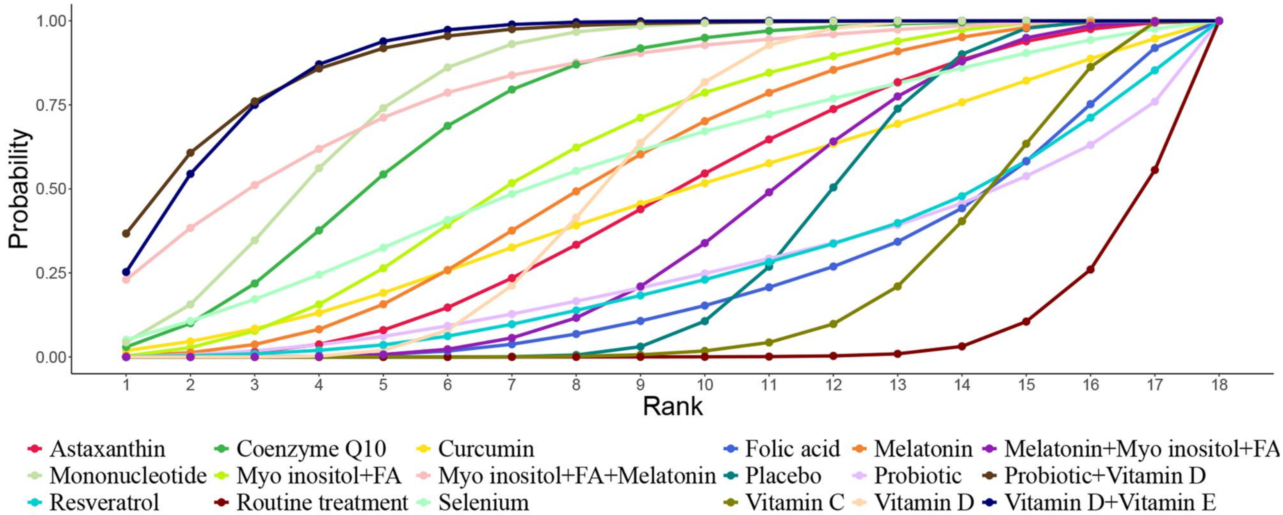
Discussion

This NMA represents the first attempt, to our knowledge, to analyze the effect of nutritional supplements on reproductive outcomes (CPR, FR, MR, NOR, NGE, MII) in infertile women, based on data from 30 eligible studies. The results revealed that compared to other interventions, the intake of probiotic + vitamin D exhibited the most significant increase in CPR. Curcumin intake alone demonstrated a substantial increase in NOR, while curcumin intake alone also led to a notable rise in FR. Furthermore, astaxanthin intake alone resulted in a substantial increase in NGE. Curcumin intake showed the most pronounced effect for increasing MII. Notably, the assessment of AEs revealed no association between any intervention and miscarriage.

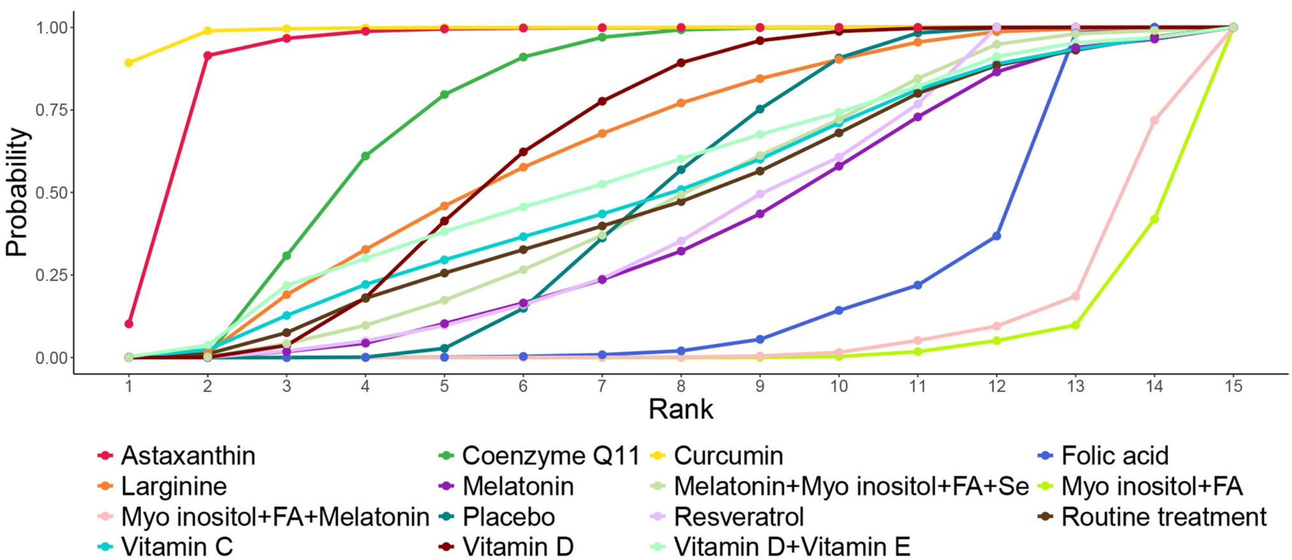
Table 2 Clinical pregnancy rates league table

Placebo																	
0.57 (0.38, 0.86)	**Routine treatment**																
1.19 (0.69, 2.09)	**2.07 (1.05, 4.13)**	**Astaxanthin**															
0.83 (0.31, 2.24)	1.44 (0.5, 4.23)	0.7 (0.23, 2.17)	**Resveratrol**														
0.81 (0.37, 1.81)	1.42 (0.59, 3.47)	0.68 (0.26, 1.81)	0.98 (0.55, 1.79)	**Folic acid**													
1.33 (0.78, 2.41)	**2.31 (1.4, 4.11)**	1.12 (0.52, 2.5)	1.61 (0.52, 5.07)	1.64 (0.63, 4.33)	**Melatonin**												
1.06 (0.77, 1.49)	**1.85 (1.1, 3.13)**	0.9 (0.47, 1.7)	1.28 (0.45, 3.62)	1.31 (0.55, 3.04)	0.8 (0.4, 1.5)	**Melatonin + Myo inositol + FA + Se**											
1.46 (0.71, 3.1)	**2.56 (1.12, 5.97)**	1.23 (0.5, 3.12)	1.77 (0.92, 3.45)	**1.8 (1.36, 2.42)**	1.1 (0.43, 2.76)	1.38 (0.63, 3.12)	**Myo inositol + FA**										
2.32 (0.81, 6.98)	**4.05 (1.31, 13.12)**	1.95 (0.6, 6.65)	**2.78 (1.03, 8.03)**	**2.84 (1.27, 6.85)**	1.74 (0.52, 5.97)	2.18 (0.72, 6.9)	1.57 (0.74, 3.63)	**Myo inositol + FA + Melatonin**									
1.29 (1.1, 1.52)	**2.25 (1.47, 3.46)**	1.09 (0.61, 1.93)	1.56 (0.57, 4.24)	1.59 (0.7, 3.52)	0.97 (0.53, 1.7)	1.22 (0.84, 1.75)	0.88 (0.41, 1.84)	0.56 (0.18, 1.61)	**Vitamin D**								
0.81 (0.61, 1.08)	**1.41 (1.03, 1.95)**	0.68 (0.36, 1.26)	0.98 (0.35, 2.72)	1 (0.42, 2.27)	0.61 (0.34, 1.04)	0.76 (0.49, 1.18)	0.55 (0.25, 1.2)	0.35 (0.11, 1.04)	0.62 (0.45, 0.87)	**Vitamin C**							
2.76 (1.67, 5.07)	**4.82 (2.53, 9.95)**	**2.33 (1.09, 5.24)**	**3.35 (1.09, 10.48)**	**3.42 (1.31, 9.06)**	2.08 (0.95, 4.6)	**2.6 (1.41, 5.16)**	1.89 (0.76, 4.78)	1.2 (0.35, 3.98)	**2.13 (1.26, 3.99)**	**3.42 (1.91, 6.66)**	**Vitamin D + Vitamin E**						
1.17 (0.44, 3.21)	2.04 (0.71, 6.05)	0.99 (0.32, 3.12)	1.42 (0.35, 5.79)	1.44 (0.41, 5.15)	0.88 (0.28, 2.75)	1.1 (0.39, 3.18)	0.8 (0.23, 2.77)	0.51 (0.12, 2.18)	0.91 (0.34, 2.52)	1.45 (0.52, 4.14)	0.42 (0.14, 1.32)	**Curcumin**					
1.84 (1.06, 3.31)	**3.21 (1.62, 6.53)**	1.55 (0.71, 3.45)	2.23 (0.71, 6.97)	2.27 (0.86, 6)	1.38 (0.62, 3.05)	1.73 (0.91, 3.39)	1.26 (0.5, 3.18)	0.8 (0.23, 2.65)	1.42 (0.8, 2.61)	**2.28 (1.22, 4.37)**	0.67 (0.29, 1.45)	1.58 (0.5, 4.86)	**Coenzyme Q10**				
0.8 (0.22, 2.29)	1.38 (0.38, 4.14)	0.67 (0.17, 2.21)	0.95 (0.19, 4.06)	0.97 (0.22, 3.63)	0.59 (0.15, 1.91)	0.75 (0.2, 2.27)	0.54 (0.12, 1.94)	0.34 (0.06, 1.52)	0.62 (0.17, 1.76)	0.98 (0.27, 2.89)	0.28 (0.07, 0.93)	0.67 (0.14, 2.88)	0.43 (0.11, 1.43)	**Probiotic**			
2.94 (1.45, 6.48)	**5.12 (2.41, 11.76)**	**2.49 (1, 6.44)**	**3.57 (1.04, 12.42)**	**3.63 (1.23, 10.87)**	2.21 (0.9, 5.57)	2.76 (1.26, 6.47)	2.02 (0.71, 5.8)	1.27 (0.34, 4.7)	2.27 (1.13, 4.96)	**3.64 (1.75, 8.2)**	1.06 (0.42, 2.7)	2.51 (0.74, 8.74)	1.6 (0.64, 4.16)	**3.69 (1.51, 12.24)**	**Probiotic + Vitamin D**		
1.43 (0.53, 4.27)	2.49 (0.86, 7.98)	1.2 (0.39, 4.05)	1.73 (0.43, 7.48)	1.76 (0.5, 6.67)	1.07 (0.34, 3.63)	1.34 (0.48, 4.2)	0.98 (0.28, 3.58)	0.62 (0.14, 2.78)	1.1 (0.41, 3.32)	1.77 (0.63, 5.48)	0.51 (0.16, 1.71)	1.22 (0.3, 5.23)	0.78 (0.25, 2.66)	1.83 (0.42, 9.48)	0.48 (0.14, 1.77)	**Selenium**	
2.09 (1.35, 3.43)	**3.65 (2, 6.86)**	1.77 (0.86, 3.65)	2.53 (0.85, 7.59)	**2.58 (1.03, 6.45)**	1.57 (0.76, 3.26)	**1.97 (1.13, 3.55)**	1.43 (0.6, 3.41)	0.91 (0.27, 2.88)	**1.61 (1.02, 2.72)**	**2.59 (1.52, 4.57)**	0.76 (0.36, 1.53)	1.79 (0.6, 5.27)	1.14 (0.55, 2.36)	2.65 (0.84, 10.24)	0.71 (0.29, 1.68)	1.47 (0.45, 4.42)	**Mononucleotide**

The data in the table are the RR (95CrI) of the intervention in the row compared to the intervention in the column. A larger RR represents a higher clinical pregnancy rate, 1 represents no difference between the two interventions. Bolding represents a statistically significant increase in clinical pregnancies rate



A：SUCRA for CPR



B：SUCRA for NOR

Fig. 5 Cumulative probability ranking plot. **A**: Clinical Pregnancy Rate (CPR), **B**: No. of oocytes retrieved (NOR)

This NMA found a significant increase in CPR in infertile women after the intake of probiotics + vitamin D. Furthermore, a significant increase in CPR was found after the intake of vitamin D or coenzyme Q10 alone, or the intake of vitamin D + vitamin E. A significant effect of vitamin D was observed in enhancing the CPR in infertile women. This finding aligns with the conclusions of previous studies. In a meta-analysis of 20 RCTs, Yang et al. showed that vitamin D significantly increased the CPR in women with PCOS [56]. Moreover, a meta-analysis by Meng et al. showed that infertile women treated with vitamin D supplements had a higher CPR than the control group [57]. A study has shown that the vitamin D receptor (VDR) is abundant in various tissues, including female ovaries, mixed ovarian cells, and purified granulosa cells [58]. The expression of VDR in these tissues suggests a role for vitamin D in sex hormone synthesis [52]. One potential explanation for this phenomenon is that vitamin D modulates the immune response by reducing Th1 differentiation and the expression of inflammatory factors such as TNF-α, thereby reducing granulosa cell inflammation [59]. Vitamin D is also found to be linked to enhanced ovulation, as well as increased endometrial thickness [60]. Additionally, the role of coenzyme Q10 in

Table 3 No. of oocytes retrieved league table

Placebo														
−0.23 (−3.92, 3.5)	**Routine treatment**													
0.7 (−1.46, 2.85)	0.92 (−3.37, 5.21)	**Larginine**												
4.12 (1.78, 6.46)	4.35 (−0.05, 8.72)	**3.42 (0.24, 6.61)**	**Astaxanthin**											
−0.58 (−2.66, 1.52)	−0.35 (−4.61, 3.9)	−1.28 (−4.27, 1.74)	−4.7 (−7.83, −1.56)	**Resveratrol**										
−2.18 (−4.25, −0.1)	−1.95 (−6.2, 2.29)	−2.88 (−5.86, 0.13)	−6.31 (−9.42, −3.17)	−1.6 (−1.84, −1.36)	**Folic acid**									
−0.66 (−3.59, 2.25)	−0.44 (−2.73, 1.83)	−1.36 (−4.99, 2.28)	−4.79 (−8.52, −1.04)	−0.08 (−3.67, 3.49)	1.52 (−2.06, 5.09)	**Melatonin**								
−0.17 (−2.23, 1.89)	0.05 (−4.19, 4.29)	−0.87 (−3.85, 2.11)	−4.29 (−7.42, −1.17)	0.41 (−2.54, 3.34)	2.01 (−0.92, 4.92)	0.49 (−3.06, 4.06)	**Melatonin + Myo inositol + FA + Se**							
−3.36 (−5.39, −1.32)	−3.13 (−7.36, 1.08)	−4.06 (−7.02, −1.08)	−7.48 (−10.57, −4.37)	−2.78 (−3.24, −2.32)	−1.18 (−1.57, −0.79)	−2.69 (−6.24, 0.86)	−3.19 (−6.08, −0.28)	**Myo inositol + FA**	−0.21 (−1.1, 0.67)					
−3.15 (−5.36, −0.93)	−2.92 (−7.24, 1.4)	−3.85 (−6.93, −0.75)	−7.27 (−10.48, −4.04)	−2.57 (−3.56, −1.56)	−0.96 (−1.93, 0.01)	−2.48 (−6.13, 1.19)	−2.98 (−6, 0.07)	0.21 (−0.67, 1.1)	**Myo inositol + FA + Melatonin**					
0.65 (−0.18, 1.49)	0.88 (−2.95, 4.67)	−0.05 (−2.35, 2.27)	−3.47 (−5.94, −0.99)	1.23 (−1.02, 3.48)	**2.83 (0.6, 5.06)**	1.32 (−1.72, 4.35)	0.82 (−1.4, 3.05)	**4.01 (1.81, 6.21)**	**3.8 (1.43, 6.17)**	**Vitamin D**				
−0.12 (−3.94, 3.71)	0.1 (−0.83, 1.03)	−0.82 (−5.21, 3.57)	−4.25 (−8.71, 0.25)	0.45 (−3.89, 4.8)	2.05 (−2.29, 6.39)	0.54 (−1.91, 3)	0.05 (−4.29, 4.38)	3.23 (−1.09, 7.56)	3.02 (−1.4, 7.43)	−0.78 (−4.68, 3.16)	**Vitamin C**			
0.3 (−3.23, 3.83)	0.52 (−4.6, 5.61)	−0.4 (−4.53, 3.76)	−3.83 (−8.02, 0.4)	0.88 (−3.23, 4.98)	2.48 (−1.63, 6.58)	0.96 (−3.62, 5.54)	0.47 (−3.6, 4.56)	3.66 (−0.43, 7.73)	3.45 (−0.73, 7.61)	−0.36 (−3.99, 3.28)	0.42 (−4.78, 5.61)	**Vitamin D + Vitamin E**		
6.96 (3.23, 10.71)	**7.19 (1.9, 12.45)**	**6.27 (1.93, 10.59)**	2.84 (−1.57, 7.26)	**7.54 (3.24, 11.84)**	**9.15 (4.85, 13.43)**	**7.63 (2.87, 12.38)**	**7.13 (2.85, 11.43)**	**10.33 (6.05, 14.6)**	**10.11 (5.74, 14.47)**	**6.31 (2.47, 10.16)**	**7.09 (1.72, 12.42)**	**6.66 (1.52, 11.81)**	**Curcumin**	
1.29 (0.6, 1.98)	1.52 (−2.27, 5.27)	0.59 (−1.66, 2.86)	−2.83 (−5.27, −0.38)	1.87 (−0.33, 4.06)	3.47 (1.29, 5.65)	1.95 (−1.04, 4.96)	1.47 (−0.72, 3.63)	**4.65 (2.5, 6.8)**	**4.44 (2.12, 6.77)**	0.64 (−0.44, 1.72)	1.42 (−2.48, 5.29)	0.99 (−2.6, 4.59)	−5.67 (−9.49, −1.86)	**Coenzyme Q11**

The data in the table are the MD (95CrI) of the intervention in the row compared to the intervention in the column. A larger MD represents a higher no. of oocytes retrieved, 0 represents no difference between the two interventions. Bolding represents a statistically significant increase in no. of oocytes retrieved

Table 4 Fertilization rate league table

Placebo										
−2.83 (−18.98, 13.27)	**Larginine**									
3.04 (−4.14, 10.15)	5.89 (−11.78, 23.55)	**Astaxanthin**								
8.19 (−55.98, 72.4)	11.05 (−55.12, 77)	5.17 (−59.42, 69.78)	**Resveratrol**							
−2.52 (−55.78, 50.86)	0.32 (−55.1, 55.99)	−5.54 (−59.32, 48.26)	−10.69 (−46.95, 25.34)	**Folic acid**						
15.79 (−37.35, 69.05)	18.63 (−36.67, 74.24)	12.77 (−40.91, 66.42)	7.61 (−28.74, 43.86)	**18.32 (14.57, 22.07)**	**Myo inositol + FA**					
18.8 (−35.31, 72.85)	21.62 (−34.67, 78.09)	15.78 (−38.87, 70.37)	10.62 (−27.32, 48.29)	**21.31 (10.46, 32.23)**	3 (−7.22, 13.27)	**Myo inositol + FA + Melatonin**				
−2 (−2.49, −1.51)	0.84 (−15.28, 16.99)	−5.03 (−12.16, 2.15)	−10.17 (−74.38, 53.98)	0.52 (−52.88, 53.77)	−17.79 (−71.04, 35.34)	−20.81 (−74.85, 33.31)	**Vitamin D**			
2.39 (−5.06, 9.89)	5.2 (−12.56, 23.02)	−0.63 (−11, 9.72)	−5.79 (−70.32, 58.61)	4.93 (−48.84, 58.55)	−13.42 (−67.13, 40.13)	−16.4 (−70.92, 38.17)	4.39 (−3.06, 11.9)	**Vitamin D + Vitamin E**		
9.02 (2.98, 15.07)	11.84 (−5.32, 29.11)	6.01 (−3.38, 15.32)	0.82 (−63.58, 65.36)	11.55 (−42.22, 64.94)	−6.78 (−60.39, 46.59)	−9.75 (−64.2, 44.58)	**11.02 (4.96, 17.08)**	6.65 (−2.99, 16.22)	**Curcumin**	
8.09 (−17.56, 33.48)	10.94 (−19.33, 41.1)	5.09 (−21.59, 31.39)	−0.23 (−69.14, 68.83)	10.62 (−48.49, 69.72)	−7.74 (−66.73, 51.37)	−10.71 (−70.66, 49.18)	10.09 (−15.56, 35.5)	5.68 (−20.98, 32.26)	−0.96 (−27.38, 25.26)	**Coenzyme Q11**

The data in the table are the MD (95CrI) of the intervention in the row compared to the intervention in the column. A larger MD represents a higher fertilization rate, 0 represents no difference between the two interventions. Bolding represents a statistically significant increase in fertilization rate

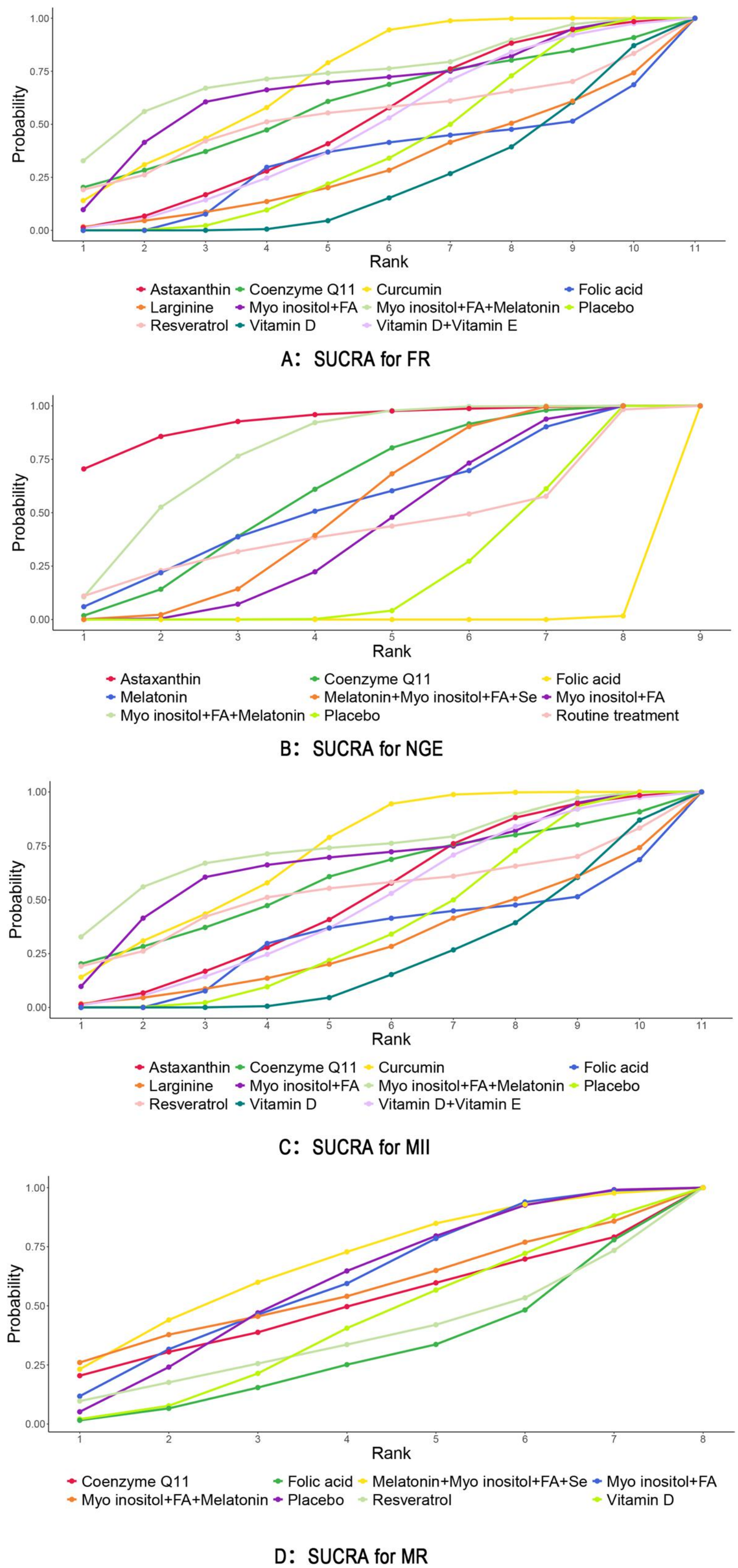


Fig. 6 Cumulative probability ranking plot. **A**: Fertilization rate (FR), **B**: No. of good-quality embryos (NGE), **C**: MII, **D**: Miscarriage rate (MR)

Table 5 No. of good quality embryos league table

Placebo	**−0.07 (−1.86, 1.7)**	**−1.17 (−2.16, −0.19)**	**1.88 (1.5, 2.27)**	**−0.32 (−1.4, 0.74)**	**−0.27 (−0.49, −0.05)**	**−0.19 (−0.51, 0.13)**	**−0.64 (−1.1, −0.17)**	**−0.38 (−0.82, 0.05)**
0.07 (−1.7, 1.86)	**Routine treatment**	−1.1 (−3.12, 0.93)	1.96 (0.15, 3.78)	−0.25 (−1.67, 1.17)	−0.2 (−1.98, 1.6)	−0.12 (−1.91, 1.69)	−0.56 (−2.39, 1.28)	−0.31 (−2.13, 1.52)
1.17 (0.19, 2.16)	1.1 (−0.93, 3.12)	**Astaxanthin**	3.06 (2, 4.11)	0.85 (−0.61, 2.29)	0.9 (−0.1, 1.91)	0.98 (−0.05, 2.02)	0.53 (−0.55, 1.62)	0.79 (−0.29, 1.86)
−1.88 (−2.27, −1.5)	−1.96 (−3.78, −0.15)	−3.06 (−4.11, −2)	**Folic acid**	−2.21 (−3.35, −1.08)	−2.15 (−2.6, −1.71)	−2.07 (−2.28, −1.87)	−2.52 (−2.92, −2.12)	−2.27 (−2.85, −1.69)
0.32 (−0.74, 1.4)	0.25 (−1.17, 1.67)	−0.85 (−2.29, 0.61)	**2.21 (1.08, 3.35)**	**Melatonin**	0.05 (−1.03, 1.15)	0.13 (−0.98, 1.25)	−0.32 (−1.48, 0.86)	−0.06 (−1.21, 1.09)
0.27 (0.05, 0.49)	0.2 (−1.6, 1.98)	−0.9 (−1.91, 0.1)	**2.15 (1.71, 2.6)**	−0.05 (−1.15, 1.03)	**Melatonin + Myo inositol + FA + Se**	0.08 (−0.31, 0.47)	−0.37 (−0.88, 0.15)	−0.11 (−0.6, 0.37)
0.19 (−0.13, 0.51)	0.12 (−1.69, 1.91)	−0.98 (−2.02, 0.05)	**2.07 (1.87, 2.28)**	−0.13 (−1.25, 0.98)	−0.08 (−0.47, 0.31)	**Myo inositol + FA**	−0.45 (−0.79, −0.11)	−0.19 (−0.73, 0.34)
0.64 (0.17, 1.1)	0.56 (−1.28, 2.39)	−0.53 (−1.62, 0.55)	**2.52 (2.12, 2.92)**	0.32 (−0.86, 1.48)	0.37 (−0.15, 0.88)	**0.45 (0.11, 0.79)**	**Myo inositol + FA + Melatonin**	0.26 (−0.38, 0.89)
0.38 (−0.05, 0.82)	0.31 (−1.52, 2.13)	−0.79 (−1.86, 0.29)	**2.27 (1.69, 2.85)**	0.06 (−1.09, 1.21)	0.11 (−0.37, 0.6)	0.19 (−0.34, 0.73)	−0.26 (−0.89, 0.38)	**Coenzyme Q11**

The data in the table is the MD (95CrI) of the intervention in the row compared to the intervention in the column. A larger MD represents a higher no. of good quality embryos, 0 represents no difference between the two interventions. Bolding represents a statistically significant increase in no. of good quality embryos

Table 6 MII league table

Placebo								
−0.86 (−2.2, 0.47)	**Larginine**							
3.3 (1.56, 5.05)	**4.17 (1.95, 6.37)**	**Astaxanthin**						
0.78 (0.24, 1.32)	**1.64 (0.2, 3.08)**	−2.52 (−4.35, −0.7)	**Resveratrol**					
−0.72 (−1.21, −0.23)	0.14 (−1.28, 1.57)	−4.02 (−5.84, −2.21)	−1.5 (−1.71, −1.28)	**Folic acid**				
0.01 (−1.99, 2)	0.87 (−1.54, 3.28)	−3.3 (−5.95, −0.63)	−0.77 (−2.84, 1.3)	0.73 (−1.33, 2.78)	**Melatonin + Myo inositol + FA + Se**			
−1.21 (−1.57, −0.84)	−0.34 (−1.73, 1.04)	−4.51 (−6.29, −2.73)	−1.98 (−2.38, −1.58)	−0.48 (−0.82, −0.15)	−1.21 (−3.23, 0.82)	**Myo inositol + FA**		
−0.41 (−1.26, 0.45)	0.46 (−1.13, 2.05)	−3.71 (−5.65, −1.76)	−1.18 (−2.06, −0.31)	0.31 (−0.53, 1.16)	−0.42 (−2.58, 1.76)	0.8 (0.02, 1.58)	**Myo inositol + FA + Melatonin**	
6.35 (3.31, 9.41)	**7.22 (3.89, 10.54)**	3.05 (−0.46, 6.56)	**5.57 (2.48, 8.68)**	**7.07 (3.99, 10.17)**	**6.34 (2.72, 9.99)**	**7.55 (4.49, 10.63)**	**6.76 (3.59, 9.94)**	**Curcumin**

The data in the table is the MD (95CrI) of the intervention in the row compared to the intervention in the column. A larger MD represents a higher MII, 0 represents no difference between the two interventions. Bolding represents a statistically significant increase in MII

Table 7 Miscarriage rate league table

Placebo							
1.96 (0.09, 42.7)	**Resveratrol**						
2.16 (0.16, 31.51)	1.09 (0.24, 5.69)	**Folic acid**					
0.82 (0.35, 1.85)	0.41 (0.02, 9.88)	0.38 (0.02, 5.75)	**Melatonin + Myo inositol + FA + Se**				
1 (0.11, 9.32)	0.51 (0.06, 4.12)	0.47 (0.1, 1.68)	1.23 (0.11, 13.26)	**Myo inositol + FA**			
1.02 (0.04, 23.14)	0.53 (0.02, 10.85)	0.47 (0.03, 6.11)	1.26 (0.05, 31.64)	1.03 (0.11, 9.23)	**Myo inositol + FA + Melatonin**		
1.33 (0.74, 2.41)	0.68 (0.03, 15.39)	0.61 (0.04, 8.83)	1.62 (0.6, 4.59)	1.33 (0.13, 13.71)	1.29 (0.05, 31.54)	**Vitamin D**	
1.21 (0.13, 11.43)	0.61 (0.01, 26.95)	0.56 (0.02, 17.04)	1.48 (0.14, 16.27)	1.21 (0.05, 28.59)	1.18 (0.03, 54.97)	0.91 (0.09, 9.22)	**Coenzyme Q11**

The data in the table is the RR (95CrI) of the intervention in the row compared to the intervention in the column. A larger RR represents a higher miscarriage rate, 1 represents no difference between the two interventions. Bolding represents a statistically significant increase in miscarriage rate

improving CPR is equally noteworthy. As an antioxidant in the mitochondrial respiratory chain, this free radical scavenger contributes to the regulation of energy metabolism [61]. One study indicates that patients undergoing IVF who achieved successful pregnancies had significantly higher mean coenzyme Q10 concentrations in their follicular fluid than those who did not [62]. In animal studies by Ben-Meir et al., the disruption of coenzyme Q10 synthesis in mice was linked to reduced ATP production and an abnormal increase in the meiotic spindle, causing infertility [63]. This finding underscores the potential of coenzyme Q10 in infertility treatment. Additionally, NMA results indicate that supplementation with vitamin D and coenzyme Q10 significantly improves CPR in infertile women compared to routine treatment. Routine treatment typically refers to a series of ovarian stimulation protocols performed prior to in vitro fertilization (IVF). This finding suggests that there may be a potential avenue for improving fertility outcomes beyond standard treatment. The purpose of ovarian stimulation is to optimize egg production, and the addition of vitamin D and coenzyme Q10 appears to produce a synergistic effect, possibly by improving oocyte quality, endometrial receptivity, or reducing oxidative stress, which are key factors for successful pregnancy [62]. Curcumin intake alone is effective in increasing the number of oocytes, mature oocytes (MII) and FR in infertile women. Curcumin, a polyphenolic compound extracted from the rhizome of turmeric, has been shown in previous studies to have multiple antioxidant [64], anti-inflammatory [65], anti-microbial [66], pro-apoptotic [67], and anti-angiogenic [64] effects. Several recent animal studies have revealed that curcumin administration promotes ovarian growth and folliculogenesis in rats [68], and attenuates d-galactose and cyclophosphamide-induced ovarian failure in mice [69, 70]. Curcumin can interact with steroid hormones and their receptors, affecting the hypothalamic-pituitary-ovarian axis [71]. These are mediated, in part, by inhibiting androgen receptors and stimulating 3-β-hydroxysteroid dehydrogenase [69]. Additionally, it can attenuate apoptosis in the ovary while promoting folliculogenesis and oocyte maturation. These effects ultimately improve fertility and fetal viability [72]. However, the number of studies on the mechanism of action of curcumin in humans, especially in pregnant women, is small. Further studies are needed to explore such mechanisms.

This NMA also revealed a significant effect of astaxanthin intake on NGE. The efficacy of astaxanthin in treating infertility has been investigated in relatively few studies. A recent meta-analysis of animal studies demonstrated that astaxanthin improved oocyte counts and antioxidant capacity in animals [73]. However, the same analysis did not find an improved effect of astaxanthin

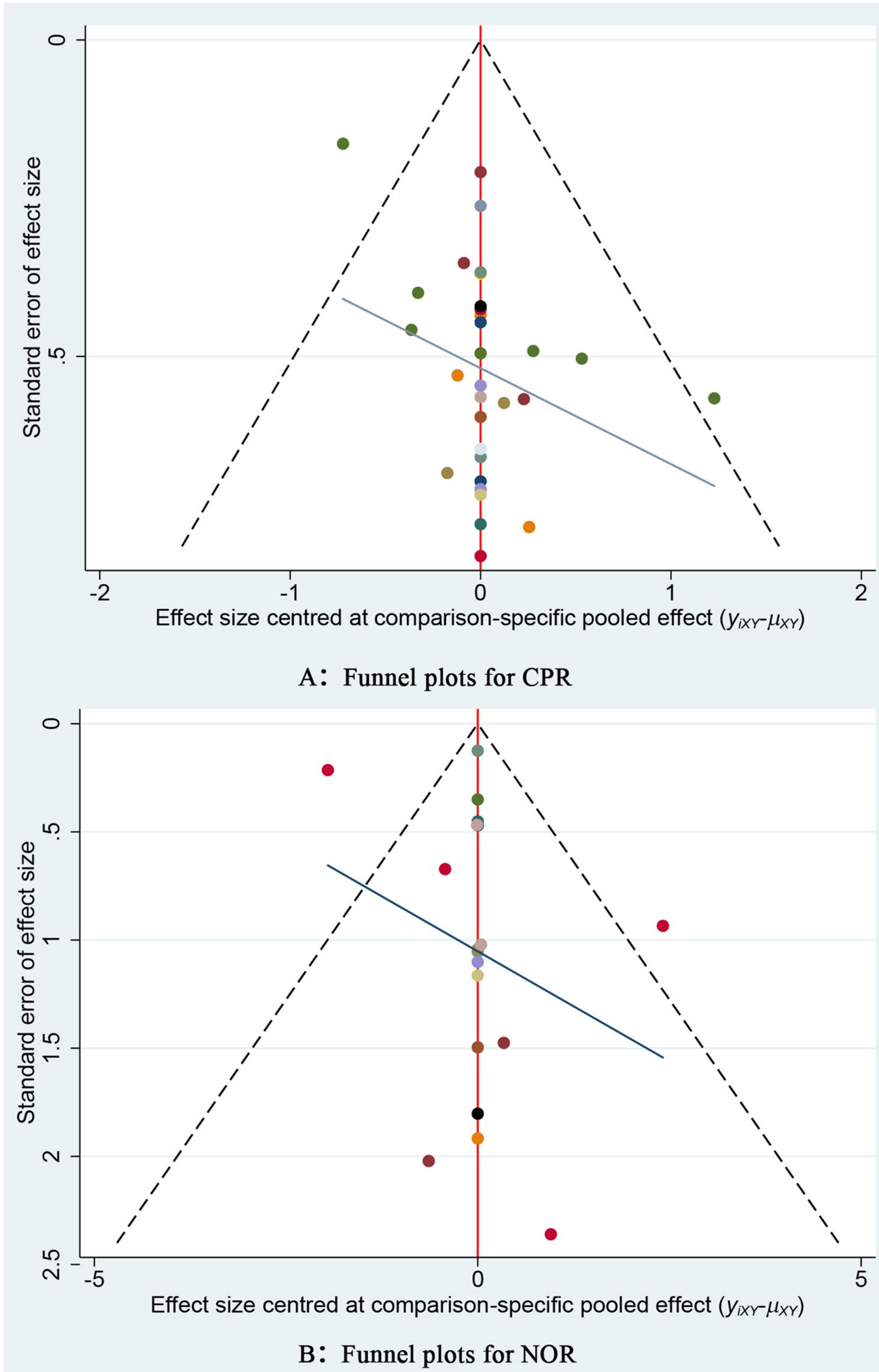


Fig. 7 Funnel plots. **A**: Clinical Pregnancy Rate (CPR), **B**: No. of oocytes retrieved (NOR)

on embryo. The efficacy of astaxanthin may stem from its antioxidant properties and modulation of inflammatory factor expression. A number of RCTs have demonstrated a significant reduction in the expression of inflammatory factors (e.g., IL-1β tumor necrosis factor-α [TNF-α], and IL-6) in infertile patients taking astaxanthin compared to placebo [30]. Furthermore, a concomitant reduction was observed in the level of oxidative stress in these patients [29]. Further clinical studies are needed to substantiate the effect of astaxanthin in infertility.

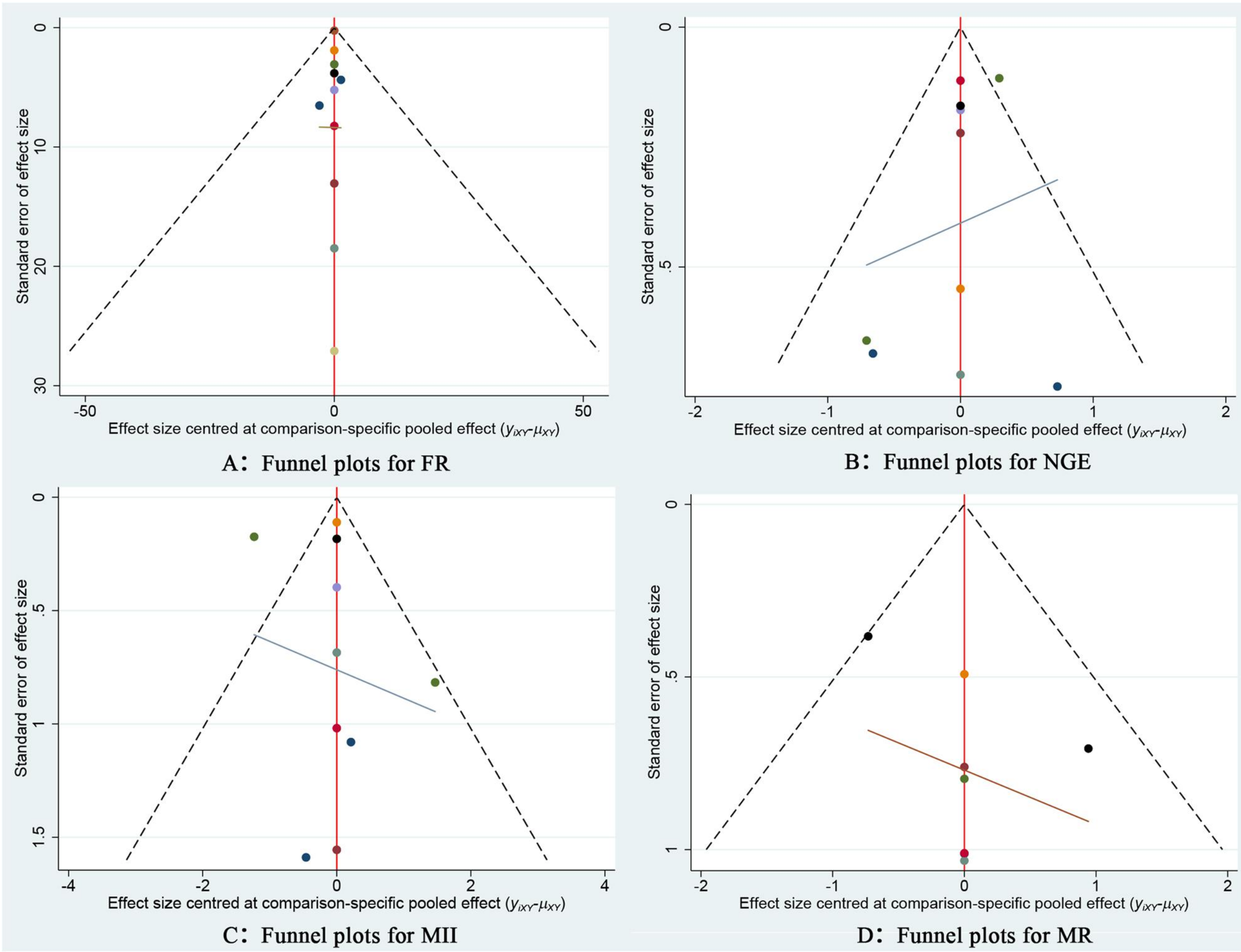


Fig. 8 Funnel plots. **A**: Fertilization rate (FR), **B**: No. of good-quality embryos (NGE), **C**: MII, **D**: Miscarriage rate (MR)

This NMA conducted an extensive search and synthesized the most comprehensive evidence to date on the use of nutritional supplements in infertile women. However, it is not without limitations. First, although it thoroughly examined all RCTs with synthesizable data, there remained a lack of available trials that could be used for direct comparisons, which might have influenced its results. Second, a significant proportion of included RCTs originated from Iran, while the number of articles from other countries and regions, particularly developed ones, was limited. This may impact the generalizability of the results. Thirdly, articles that were not mentioned in this NMA due to non-blinding of patients or allocation concealment might have an impact on the overall quality assessment. Fourthly, the analysis on the safety of nutritional supplements only included MR, which did not allow for a comprehensive assessment of the possible adverse effects. In the future, multicenter, large-sample RCTs should be conducted to validate the efficacy of nutritional supplements on female infertility and to explore possible regional and ethnic differences to improve the generalizability of treatment results. Additionally, it is essential to monitor for any potential pregnancy complications. This will help to guarantee the safety of nutritional supplements as a treatment option.

Conclusions

In summary, some nutritional supplements may help improve reproductive outcomes, but the evidence for safety remains uncertain due to limited and heterogeneous data. Particularly, the combination of vitamin D and other nutritional supplements, as well as the intake of coenzyme Q10, astaxanthin, or curcumin, was more effective compared to other nutritional supplements. The results should be considered with circumspection, given the lack of direct comparative studies for most nutritional supplements. In addition, the certainty of outcomes related to safety is low. Further RCTs are needed to examine the effectiveness of these supplements and related mechanisms, and to report more safety-related outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01466-0.

Supplementary Material 1: Figure S1. Density maps for the diagnosis of convergence (clinical pregnancy rate).

Supplementary Material 2: Figure S2. Density maps for the diagnosis of convergence (Fertilization rate).

Supplementary Material 3: Figure S3. Density maps for the diagnosis of convergence (MII).

Supplementary Material 4: Figure S4. Density maps for the diagnosis of convergence (Miscarriage rate).

Supplementary Material 5: Figure S5. Density maps for the diagnosis of convergence (No. of good quality embryos).

Supplementary Material 6: Figure S6. Density maps for the diagnosis of convergence (No. of oocytes retrieved).

Supplementary Material 7: Figure S7. Results of the node splitting method of analysis (clinical pregnancy rate).

Supplementary Material 8: Table S1. The search strategy.

Supplementary Material 9: Table S2. Certainty of evidence (CINeMA results).

Acknowledgements

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Writing - original draft preparation: Jihang Du; Writing - review and editing: Qianxue Liu; Conceptualization: Jia Liu; Methodology: Chaoliang Li; Formal analysis and investigation: Jihang Du; Funding acquisition: Xiaoyan Zheng; Resources: Hao Zhu; Supervision: Jie Yang, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This study was funded by the National Natural Science Foundation of China (82174517).

Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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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Received: 27 June 2025 / Accepted: 11 August 2025
Published online: 18 November 2025

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