Review Article

Efficacy and safety of *Oxalobacter formigenes* in patients with primary hyperoxaluria: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background and Objective: Primary hyperoxaluria (PH), a rare autosomal recessive disorder, results in defective metabolism of oxalate, leading to increased oxalate levels. *Oxalobacter formigenes* (*O. formigenes*) is a nonpathological anaerobic bacterium that uses oxalate for its survival and thus decreases the plasma oxalate levels. We aimed to use randomized controlled trials (RCTs) to evaluate the efficacy of *O. formigenes* in treating PH.

Methods: A literature review was conducted for synthesizing the evidence from RCTs on Scopus, Web of Science, Embase, PubMed, and CENTRAL until January 2023. The outcomes were pooled using mean difference (MD) for continuous data and odds ratios (OR) for dichotomous data along with confidence interval (CI). The systematic review is registered with Prospero ID CRD42023404421.

Results: We included five RCTs with 208 patients. The pooled analysis did not favor *O. formigenes* over placebo in reducing the plasma oxalate levels (MD: –0.00 mmol/day; 95% CI: [– 0.01–0.00]; $P = 0.06$). Similar results were observed for urinary oxalate levels (MD: –0.01 mmol/day; 95% CI: [– 0.12–0.10]; $P = 0.86$). There were no significant adverse events (OR: 0.44; 95% CI: [0.14–1.39]; $P = 0.16$) or serious adverse events (OR: 0.80; 95% CI: [0.29–2.25]; $P = 0.67$).

Conclusion: *O. formigenes* was ineffective in reducing the serum and urine oxalate levels in patients with PH but has an acceptable safety profile. As PH is a relatively rare disease and few patients consent for the trials, stringent protocols are required in the future to achieve data accuracy pertinent for making conclusive recommendations on the efficacy of *O. formigenes* in patients with PH.

INTRODUCTION

Primary hyperoxaluria (PH), a rare autosomal recessive disorder, results in defective metabolism of oxalate and increased serum oxalate levels.[1] Manifestation of PH is variable and, depending on the levels of oxalate and the rate of progression, it can lead to end-stage renal disease.[2] Symptoms typically appear in the pediatric population, with most patients showing the signs by the age of 10, although elevated oxalate levels are often present from

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the birth. Among the three types of PH (type 1, 2, and 3), type 1 is the most severe and is caused by the deficiency or mislocalization of different enzymes that impair the hepatic oxalate production.[1,3,4] Despite its rarity, diagnostic delays may underestimate the actual incidence of the disease. Type 1 PH has an estimated prevalence of one to two cases per million, with an average incidence rate of about 0.1–0.15 per million per year, as reported by surveys of nephrologists and urologists in France, Switzerland, and The Netherlands.[5-7] Recent advances in genetic testing have highlighted the critical role of early diagnosis of monogenic kidney stone diseases like PH.[8]

A large portion of renal stones are composed of calcium, either calcium oxalate or calcium phosphate. The main underlying cause, worldwide, is hypercalciuria, whereas hypocitraturia is also recognized in the eastern hemisphere.[9] Dietary and environmental factors play a major role in stone formation; however, recurrences can be prevented through general measures.[10] Pharmacological intervention is required in high-risk patients suffering from recurrent stone formation. An ideal choice would be a drug that halts stone formation with no side effects and optimal results.[10,11]

Current conservative treatment modalities include increased fluid intake, oral inhibitors of crystal formation (citrate, magnesium, or phosphate), and pyridoxine (effective in some patients with PH type 1).[1,3,12] However, the only curative options for PH type 1 is combined liver and kidney transplantation, which carry its own risks and consequences.[13] Emerging RNA interference-based therapies such as Lumasiran offer a promising alternative by directly targeting the hepatic oxalate production, with a Phase III clinical trial demonstrating significant reduction in the urinary and plasma oxalate levels and improved clinical outcomes, providing hope for the better management of PH type 1 without the need for transplantation.[14]

Despite their potential benefits, conservative treatment modalities have limited efficacy, as they cannot prevent renal failure.[14] In patients receiving treatment, oxalate elimination often fails to outpace its increased production, leading to systemic calcium oxalate deposition.[15] The major portion of oxalate elimination from the body occurs through kidneys, whereas some occurs through the gastrointestinal tract as well.[16] *Oxalobacter formigenes* (*O. formigenes*), a non-pathological anaerobic bacterium normally present in the human intestine, uses oxalate for its survival. *O. formigenes* decreases the oxalate plasma concentration by secretion of oxalate from plasma through solute carrier anion transporter and solute-linked carrier 26, which are the carriers and channels involved in transporting ions such as oxalate into the intestine and their excretion from the body.[17-19]

O. formigenes was seen to play an important role in the management of PH by reducing oxalate levels in both urine and plasma by increasing the excretion of endogenous oxalate through the intestinal pathway. To evaluate its effectiveness, we synthesized cumulative evidence by pooling the data from existing trials.[10,14,20-22] This meta-analysis aimed to evaluate the efficacy and safety of *O. formigenes* in the treatment of PH.

METHODOLOGY

Protocol registration

The Preferred Reporting Items for Meta-Analyses (PRISMA) guidelines[23] were followed for this meta-analysis. We prospectively registered our protocol in the International Prospective Register of Systematic Reviews (PROSPERO) with ID CRD42023404421.

Data source and search strategy

An electronic search of PubMed, Scopus, Embase, and Web of Science was conducted from their inception to January 2023 without any language restrictions. The following search string was used: (Oxalobacter OR Oxalobacter Formigenes OR Oxalobacter Vibrioformis) AND (Hyperoxaluria OR "Primary hyperoxaluria" OR "High Urinary Oxalate"). In addition, we manually screened the reference list of retrieved trials, and review articles to identify any relevant studies.

Study selection

Studies retrieved using the search strategy were exported to the Covidence,[24] following which the duplicates were screened and removed. The remaining studies were meticulously assessed by two independent reviewers in accordance with the eligibility criteria. All studies were initially short-listed based on the title and abstract, following which full-length articles were reviewed. A third investigator aided in resolving any discrepancies between the selected studies.

Eligibility criteria

The following eligibility criteria were used to select the studies: (a) published randomized controlled trials (RCTs) that included patients with hyperoxaluria (type 1, 2, or 3) with a minimum treatment duration of 4 weeks; (b) studies that investigated *O. formigenes* formulations with the minimum dose of 10^7 colony-forming units; (c) studies that included twice daily dosage of *O. formigenes* in the intervention group and placebo or usual treatment in the control group; (d) studies that reported urinary or plasma oxalate levels, any adverse events, serious adverse events, and systemic adverse events including respiratory, nervous, or renal adverse events among others as the outcomes.

Data extraction

The following primary outcomes were extracted from the selected studies: (a) Urinary oxalate at the baseline and following treatment, and (b) any serious adverse

event reported following therapy. The secondary outcome extracted was plasma oxalate at the baseline and following treatment.

Risk of bias and certainty of evidence

The modified Cochrane Collaboration's risk of bias tool (RoB2) for RCTs was utilized to assess the quality of the selected studies.[25] A leave-one-out sensitivity analysis was conducted to isolate any single study responsible for outcomes where significant heterogeneity was observed. To investigate the certainty of evidence, Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[26,27] recommendations were followed, considering inconsistency, imprecision, indirectness, publication bias, and risk of bias. The evaluation was carried out for each outcome, and the decisions were justified and documented. Any discrepancies were settled through discussion.

Statistical analysis

RevMan (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all statistical analyses. The results from trials were presented as odds ratios (OR) for dichotomous outcomes and mean difference (MD) for continuous outcomes with a 95% confidence interval (CI) and were pooled using a fixed-effects model in case of homogenous data and random-effects model in case of heterogenous data. Heterogeneity across studies was evaluated using Higgins I^2 and a value <50% for I^2 was considered acceptable. Finally, Begg's test and a visual inspection of the funnel plot were conducted to evaluate the publication bias. A $P < 0.05$ was considered statistically significant.

RESULTS

Study selection and characteristics

Our initial search identified 710 studies, of which 358 studies were shortlisted for title and abstract evaluation after 352 duplicates were removed. Finally, 21 studies were selected for the full-text review, out of which five were included in the final qualitative and quantitative analyses. Further details can be obtained from the PRISMA flowchart in Figure 1.

All studies were RCTs[10,14,20-22] with a cumulative of 208 patients. Both the *O. formigenes* and placebo groups were administered as capsules twice daily with meals. The duration of follow-up among the studies ranged from 4 weeks to 52 weeks. Urinary oxalate levels were determined through 24 h urine samples and plasma oxalate levels by blood samples collected at the baseline and follow-up. The mean age of the patients in the *O. formigenes* group was 25.1 years (range: 12.9–42.6), whereas the mean age in the control group was 25.9 (range: 13.43–40.5). Most of the patients in both the *O. formigenes* cohort (58.9%) and the control cohort (57.7%) were males. Further baseline and summary characteristics of the included RCTs are outlined in Tables 1 and 2.

Quality assessment

Quality assessment of the included RCTs was conducted using the RoB2 tool. Through this tool, five domains of bias were assessed, including biases in randomizing the patient groups, randomizing the patient data, blinding of the participants and researchers, outcome measures, and reporting the outcomes. All of the studies demonstrated low overall risk of bias, rendering reliability to the pooled results [Figure 2].

Efficacy outcomes

O. formigenes did not have any significant effect on the plasma oxalate levels (MD: –0.00 mmol/day; 95% CI: [– 0.01–0.00]; $P = 0.06$). Results could be considered reliable since no significant heterogeneity was observed ($I^2 = 0\%$; $P = 0.43$) [Figure 3a].

No significant changes in the urinary oxalate levels were observed at 4 weeks (MD: 0.06 mmol/day; 95% CI: [– 0.32–0.44; $P = 0.75$]; $I^2 = 0\%$), 8 weeks (MD: 0.09 mmol/day; 95% CI: [– 0.07–0.25]; $P = 0.26$; $I^2 = 0\%$), and 24 weeks (MD: –0.17 mmol/day; 95% CI: [– 0.36–0.02]; $P = 0.08$; $I^2 = 0\%$). Overall, there were no significant differences observed between these subgroups ($P = 0.11$) [Figure 3b].

Safety outcomes

A total of three studies reported adverse events, whereas the serious adverse events were reported by four. There were no significant adverse events (OR: 0.44; 95% CI: [0.14–1.39]; $P = 0.16$) or serious adverse events (OR: 0.80; 95% CI: [0.29–2.25]; $P = 0.67$) [Figure 4].

Finally, we analyzed the data for systemic adverse events reported in the included studies. There were no significant adverse events reported for most of the systems including the gastrointestinal (OR: 0.63; 95% CI: [0.29–1.33]; $P = 0.22$), renal and urinary (OR: 0.86; 95% CI: [0.36–2.1]; $P = 0.75$), respiratory (OR: 0.75; 95% CI: [0.20–2.76]; $P = 0.66$), and musculoskeletal system (OR: 0.78; 95% CI: [0.21–2.83]; $P = 0.70$). Furthermore, no adverse systemic infections were reported (OR: 0.78; 95% CI: [0.37–1.63]; $P = 0.5$). However, while nervous system-related adverse events were recorded (OR: 0.13; 95% CI: [0.02–0.85]; $P = 0.03$), the studies did not provide specific details or further characterization of these events. Results could be considered reliable since the overall heterogeneity was very low and insignificant ($I^2 = 0\%$, $P = 0.57$) [Figure 5].

Publication bias and quality assessment

Inverted funnel plots [Supplementary Figures S1-S3] were used to visually check for the publication bias. No evidence for any potential bias could be found since the data points showed symmetry. All the studies showed a low risk of bias. The risk of bias is illustrated in Supplementary Figures S1-S3.

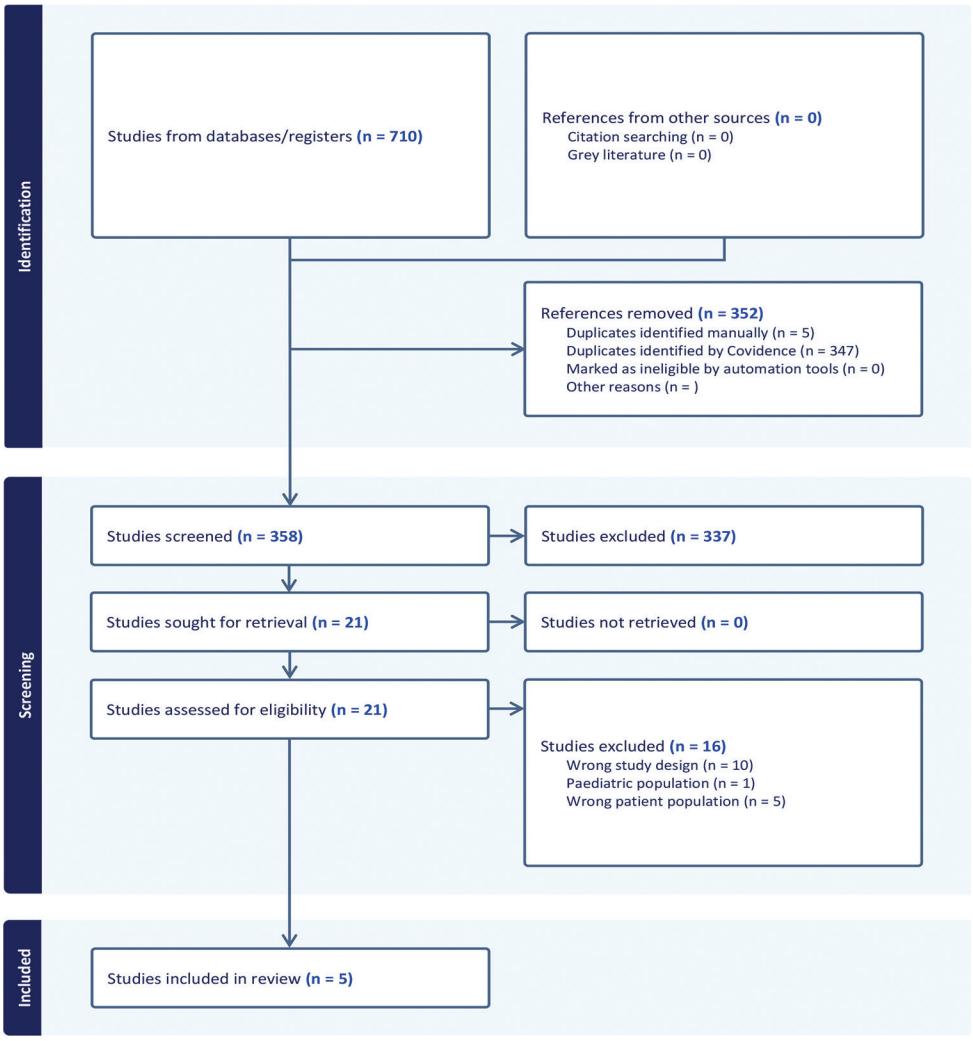

Figure 1: Preferred Reporting Items for Meta-analyses flow chart of the screening process

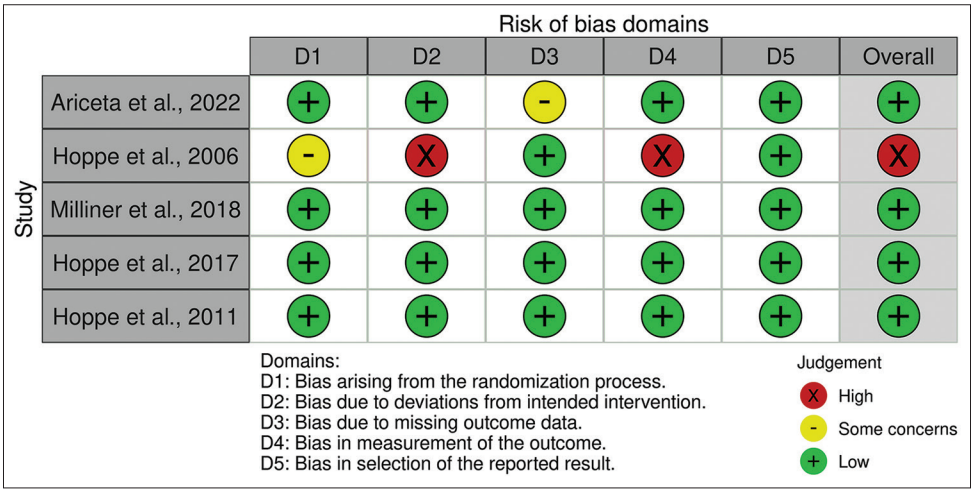

Figure 2: Cochrane risk of bias for randomized controlled trials

DISCUSSION

The aim of this meta-analysis was to evaluate the clinical course of patients presenting with PH when receiving *O. formigenes* as capsules of either OC3 (a lower-concentration formulation of *O. formigenes*) or OC5 (a higher-concentration formulation of *O. formigenes*) twice daily versus a placebo. The intrinsic ability of *O. formigenes*

Table 1: Baseline characteristics

Study ID	Number of patients in each group		Age (years), mean (SD)		Gender (male), *n* (%)		eGFR (mL/min/1.73 m²), mean (SD)	
	Oxabact	Control	Oxabact	Control	Oxabact	Control	Oxabact	Control
Ariceta *et al*., 2023[15]	13	12	12.9 (6.4)	18.31 (6.5)	4 (30.8)	7 (58.3)	70.3 (11.6)	62.4 (16.9)
Hoppe *et al*., 2011[20]	19	23	13.4 (6.47)	14.4 (6.99)	11 (57.9)	8 (34.8)	121.5 (44.58)	105.2 (29.97)
Ubaid Khan *et al*., 2017[21]	14	14	15.64 (5.39)	13.43 (5.84)	10 (71.4)	5 (35.7)	97.471 (39.666)	123.111 (45.425)
Jairath *et al*., 2015[10]	40	40	42.6 (12.14)	40.5 (16)	28 (70)	31 (77.5)	N/A	N/A
Ubaid Khan *et al*., 2018[22]	21	15	16.2 (12.72)	22.6 (16.55)	10 (47.6)	9 (60.0)	111.6 (48.60)	109.6 (40.26)

Study ID	Uox excretion (mmol/24 h/1.73 m²), mean (SD)		Number of kidney stone events in last 3 years, *n* (%)		Time since diagnosis (years), mean (SD)	
	Oxabact	Control	Oxabact	Control	Oxabact	Control
Ariceta *et al*., 2023[15]	2.107 (0.929)	1.759 (0.937)	9 (69.3)	11 (58.3)	8.41 (6.258)	4.508 (3.175)
Hoppe *et al*., 2011[20]	1.78 (0.6)	1.76 (0.64)	N/A	N/A	7.3 (5.8)	9.4 (6.0)
Ubaid Khan *et al*., 2017[21]	1.733 (0.488)	1.737 (0.696)	N/A	N/A	8.748 (5.8)	9.201 (5.26)
Jairath *et al*., 2015[10]	0.57 (0.14)	0.58 (0.13)	N/A	N/A	N/A	N/A
Ubaid Khan *et al*., 2018[22]	1.88 (0.50)	1.62 (0.52)	2.0 (3.53)	1.7 (2.05)	5.50 (6.08)	15.44 (11.96)

Uox=Urinary oxalate, eGFR=Estimated glomerular filtration rate, SD=Standard deviation, N/A=Not available

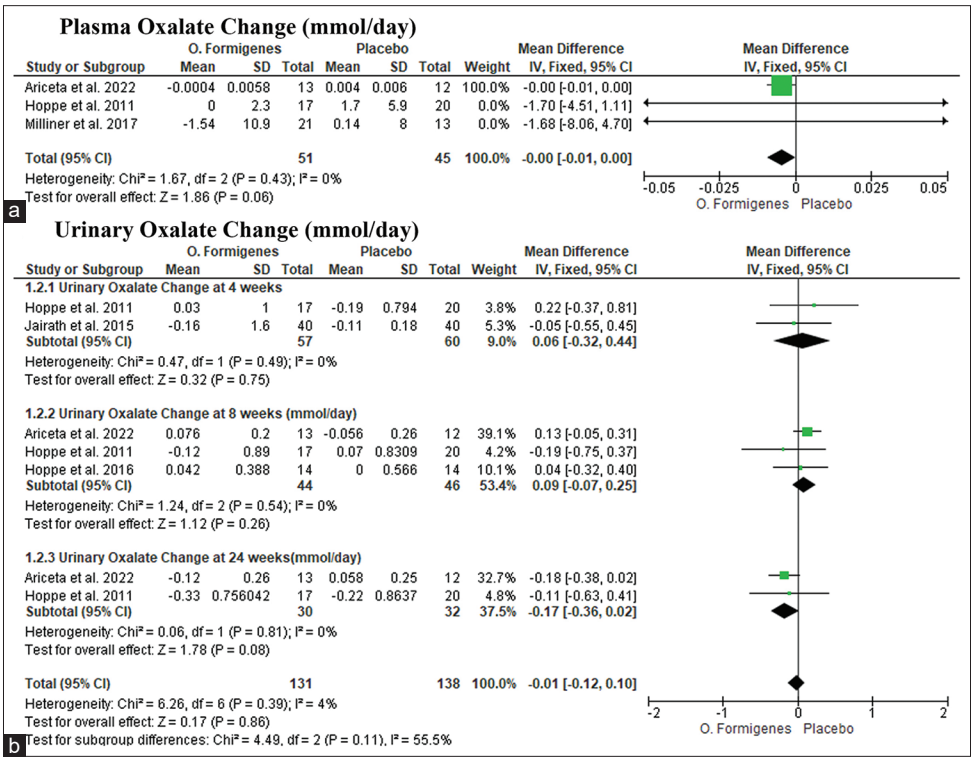

Figure 3: (a and b) Forest plot showing changes in plasma oxalate and urinary oxalate levels in *Oxalobacter formigenes* and placebo groups

to metabolize free plasma oxalate served as the foundation of this treatment approach.[16,28] Our data suggests that *O. formigenes* species, which were postulated to carry the potential to metabolize plasma oxalate and thus reduce the urinary oxalate levels, had no statistically significant effects on the plasma or urinary oxalate levels. This treatment modality was well tolerated by most of the human subjects, with a modicum of adverse events reported. These results contrast sharply with animal studies, such as those in rats, which showed optimal intestinal oxalate degradation, following either natural or artificial colonization of the colonic intraluminal space.[17,18,29] These deviations may be attributed to the physiological differences between humans and animal models, viability of *O. formigenes* species in the administered capsules, and inaccuracies in urine sample collection.

This meta-analysis evaluated the OC3 and OC5 drug classes with varying efficacies based on the viability of *O. formigenes* species. A *post-hoc* analysis by Milliner *et al.* showed an increase in the plasma oxalate levels in the placebo group compared to a stable-to-decreased levels in the OC3 group. However, these findings could not be confirmed due to the short follow-up duration and reduced survival rate and

Table 2: Study characteristics

Study ID	Study design	Country	Total participants	Oxabact			Control	
				Dose	Time of administration/day	TTT duration	Drug	Dose/times of administration
Ariceta *et al*., 2023	Phase III, double-blind, placebo-controlled, randomized, multicenter study	Belgium, France, Germany, Netherlands, United Kingdom, Spain, USA, Tunisia	24	Lyophilized *O. formigenes*, strain HC-1 (≥ 10^9–<5^{10} CFUs per dose)	One capsule twice daily with breakfast and dinner	52 weeks	Placebo	One capsule twice daily with breakfast and dinner
Hoppe *et al*., 2011	Double-blind, randomized, placebo-controlled, multicenter study	Germany, USA, UK, France, Netherlands	42	NLT 10^7 CFU of Oxabact	One capsule twice daily with meals	24 weeks	Placebo	One capsule twice daily with meals
Hoppe *et al*., 2017	Randomized, placebo-controlled, double-blind study	France, Germany, and UK	28	≥109 CFUs	One capsule twice daily with meals	8 weeks	Placebo	One capsule twice daily with meals
Milliner *et al*., 2018	Randomized, placebo-controlled, double-blind study	Germany, the Netherlands and the USA	34	A 500-mg dose of OC3 consisted of one sachet of lyophilized *O. formigenes* strain HC-1 (not < 107 CFU/dose	One sachet of OC3 powder + one sachet of buffer in water 30–60 min before meal twice daily	24 weeks	Placebo	One sachet of placebo + one sachet of buffer 30–60 min before meals twice daily
Jairath *et al*., 2015	Randomized controlled study	India	80	*O. formigenes* 700 million, L. acidophilus 400 million, *L. rhamnosus* 300 million, *B. lactis* 300 million	One capsule twice a day	1 month	KMgCit preparation	30 mEq twice a day

Study ID	Method of measurement		Hyperoxaluria type	Main inclusion criteria	Primary outcome	Follow-up duration
	Urinary oxalate	Plasma oxalate				
Ariceta *et al*., 2023	24-h urine samples at baseline and 8, 24, 40, and 52 weeks	Blood samples at baseline and every 8 weeks up to 52 weeks	1, 2, or 3	Age ≥2 years, diagnosis of PH, maintained kidney function below the lower limit of the normal range, no risk for dialysis, and total Pox concentration ≥10 μmol/L	Change in baseline total Pox concentration after 52 weeks of treatment	52 weeks
Hoppe *et al*., 2011	Three consecutive 24-h urine collections at screening (baseline, week 0) and two consecutive collections at weeks 4, 8, 12, 18, and 24	Blood samples at screening, weeks 12 and 24	1, 2, or 3	Subjects with a confirmed diagnosis of PH and >5 years of age, with a urinary oxalate excretion >1.0 mmol/1.73 m^2/day and with eGFR ≥50 mL/min/1.73 m^2 BSA were eligible for the study	Percent change in urinary oxalate from screening to week 24	24 weeks
Hoppe *et al*., 2017	Four 24-h urine collections were made at weekly intervals at baseline, and 24-h urine samples at treatment weeks 2, 4, 6, and 8	Plasma samples at weeks 4 and 8	1, 2, or 3	Male or female patients were ≥2 years of age (≥5 years in the UK) with a diagnosis of PH type 1, 2, or 3, with an eGFR of ≥40 mL/min/1.73 m^2	Absolute change in urinary oxalate excretion (mmol/24 h/1.73 m^2) from baseline to treatment week 8	8 weeks
Milliner *et al*., 2018	Two 24-h urine samples were collected at week 8, week 16, and week 24	Plasma oxalate concentration at baseline and week 24	1, 2, or 3	Patients were of either gender, aged 2 years or above and had a diagnosis of PH, urinary oxalate excretion equal to or more than 1.0 mmol/24 h/1.73 m^2, and eGFR more than 40 mL/min/1.73 m2 or a creatinine clearance equal to or more than 40 mL/min/1.73 m^2	Percentage change in urinary oxalate (expressed as molar oxalate to creatinine ratio) from baseline to week 24	24 weeks

Contd...

Table 2: Contd...

Study ID	Method of measurement		Hyperoxaluria type	Main inclusion criteria	Primary outcome	Follow-up duration
	Urinary oxalate	Plasma oxalate				
Jairath *et al.*, 2015	24-h urine samples at baseline and 1 month	N/A	1, 2, or 3	All adult patients with calcium oxalate stones were included except for those with inflammatory intestinal disease or urinary tract infection, and those undergoing antibiotic treatment	Early effect of the administration of *O. formigenes* in the metabolic pattern of patients with calcium oxalate stones	4 weeks

O. formigenes=*Oxalobacter formigenes*, *L. acidophilus*=*Lactobacillus acidophilus*, *L. rhamnosus*=*Lacticaseibacillus rhamnosus*, *B. lactis*=*Bifidobacterium lactis*, PH=Primary hyperoxaluria, CFUs=Colony-forming units, eGFR=Estimated glomerular filtration rate, BSA=Body surface area, N/A=Not available, NLT=Not Less Than, TTT=total treatment time

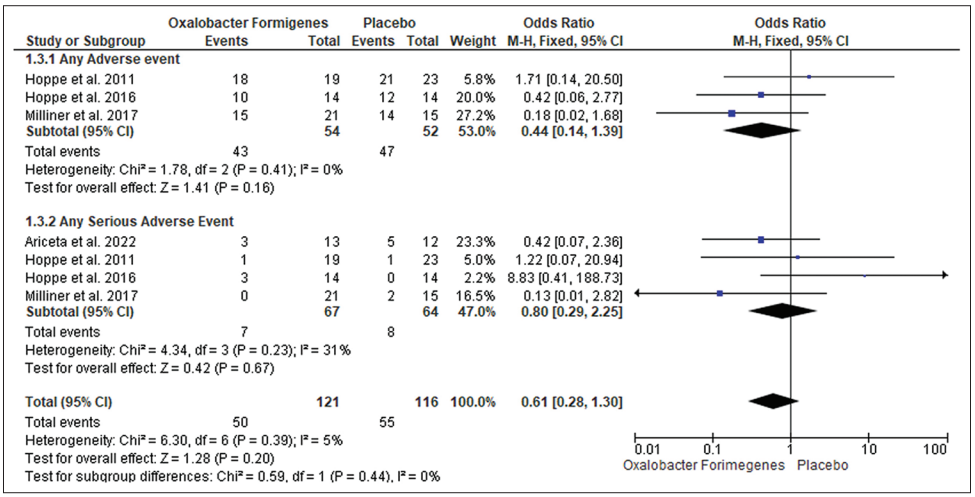

Figure 4: Forest plot showing any or serious adverse events in *Oxalobacter formigenes* and placebo groups

activity (low viability) of *O. formigenes* in the administered capsules, which may have affected the treatment's efficacy. It is hypothesized that the insensitivity of the human intestinal epithelium to the *O. formigenes* genes may explain these findings, as a study has documented that human intestinal epithelium is not responsive to *O. formigenes*.[22] Improvements in the drug design, aimed at increasing its viability and bacterial recovery, led to the development of the OC5 formulation. Hoppe *et al.*[20] incorporated these drug enhancements in their Phase I/II trial; however, no significant reduction in the urinary oxalate level was observed despite the evidence of better proliferative levels of *O. formigenes* species and higher tolerance levels. *Post hoc* analysis identified that the OC5 cohort had lower estimated glomerular filtration rate (eGFR) and higher prevalence of renal disorder compared to the placebo group. Research has shown a notable inverse relationship between eGFR and plasma oxalate levels, which may have impacted the results.[30] Differences in the baseline eGFR, along with varying disease severity, could introduce bias in the outcome assessment. In fact, advanced stages of chronic kidney disease, characterized by low eGFR, have been associated with increased oxalate deposition and reduced urinary oxalate excretion. A major limitation is the difficulty in collecting urine samples from pediatric patients. Following Hoppe *et al.*'s[20] Phase I/II trial, the capsular coat was changed from gelatin to hydroxypropyl-methylcellulose with a hope of superior *O. formigenes* strain delivery to the target intestinal region. Unfortunately, an improvement in the viability was not observed, and the dissolution down in the intestinal tract was inconsistent.[20] In our study, adverse events categorized under the gastrointestinal, nervous system, respiratory, renal and urinary, musculoskeletal, and infections did not show significant differences between *O. formigenes* and placebo or usual care, except for nervous system-related adverse events. *O. formigenes* was associated with a reduction in the nervous system-related adverse events compared to the placebo or the usual care group. Jiao *et al.* in 2024 has reported beneficial effects of metabolome and microbes on the human nervous system, showing that neuroactive metabolites, enriched in long-lived individuals, correlated with specific gut microbes, including *O. formigenes*. These metabolites were linked to enhanced brain connectivity, contributing to cognitive preservation.[31]

Strengths and limitations

Key strengths of this review include: (1) strict application of the PRISMA guidelines, (2) the first meta-analysis of

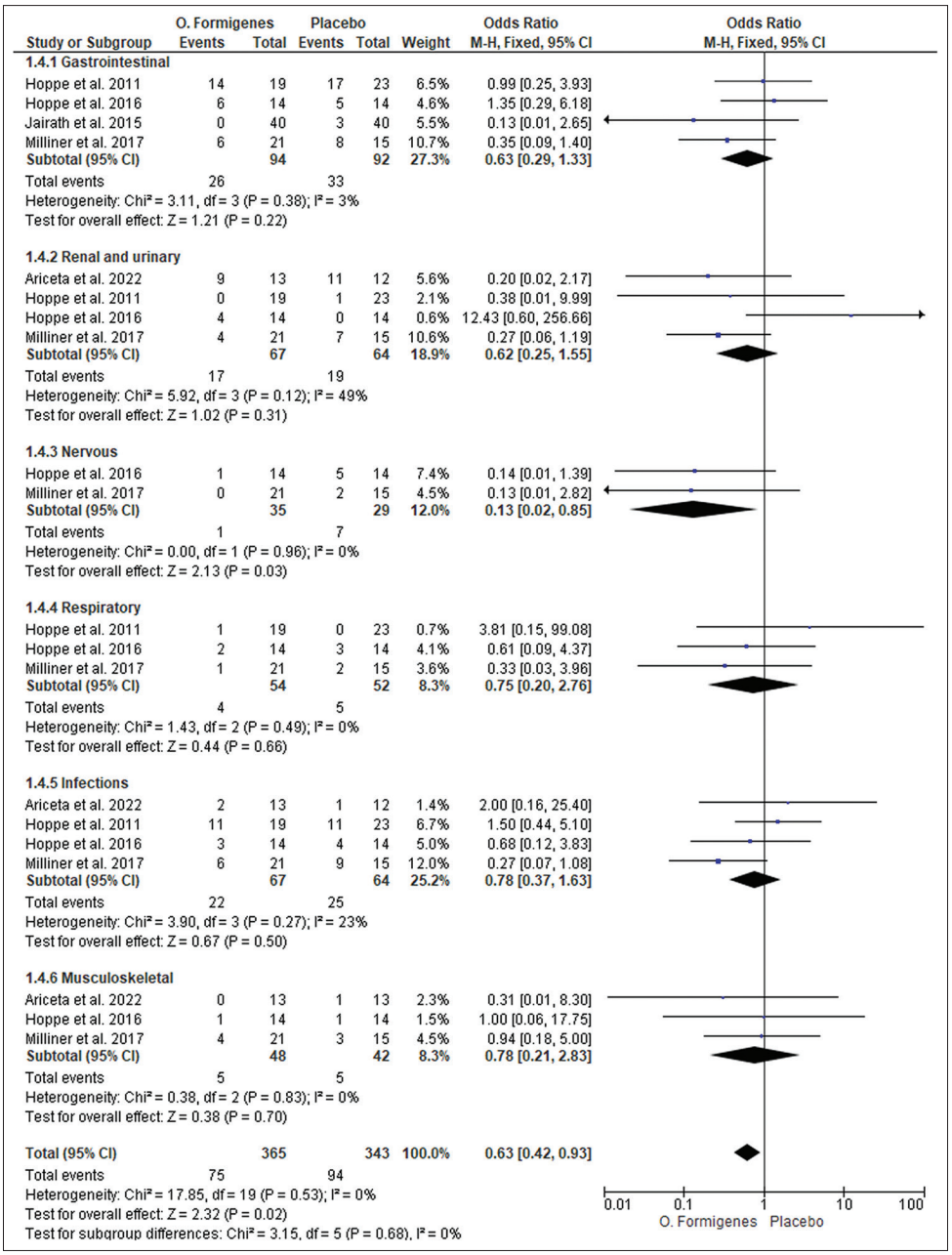

Figure 5: Forest plot showing individual systemic adverse events in *Oxalobacter formigenes* and placebo groups

RCTs that evaluated *O. formigenes* for PH eliminating any potential sources of bias; therefore, constituting the gold-standard evidence in this regard, (3) the low level of heterogeneity made the results reliable, and (4) the multicenter nature of patients' recruitment, allowing for greater representativeness and more convincing results. However, some limitations remain: (1) the small number of patients available for the analysis considering the relative rarity of the disease, and (2) the high variance in the baseline characteristics between the intervention and control cohorts.

Implications for future research

Future trials need to have longer follow-up to ensure an accurate assessment of the changes in the urinary and plasma oxalate levels. Considering the significant association between baseline patient characteristics and outcomes, experts should select cohorts stratified by their baseline renal function. Since PH is a relatively rare disease with few patients readily consenting to take part, accurate methodical approach and execution are pertinent to efficient resource utilization.

CONCLUSION

Our analysis, based on the available RCTs, found no conclusive evidence that *O. formigenes* use significantly reduces the urinary or plasma oxalate levels in patients with PH. The lack of statistically significant results highlights the

need for further research, particularly with longer follow-up and larger patient cohorts, to fully assess the potential of *O. formigenes* as a therapeutic option. Given the challenges of studying a rare disease, future trials should focus on refining the study design and ensuring more accurate and reliable results.

Author contributions

The idea was conceived by M.A., while the research workflow was designed by U.K.B. and M.Z.K. Database searches were conducted by U.K. and M.M. Screening of retrieved records, data extraction, assessment of evidence quality, and conflict resolution were carried out by J.I., N.U.A., M.N.N., and M.M., with conflicts being resolved by A.M. Analysis was performed by U.K. The final manuscript was written by M.N.N., M.M., and J.I. under the supervision of M.A. All authors have reviewed and approved the final version of the manuscript.

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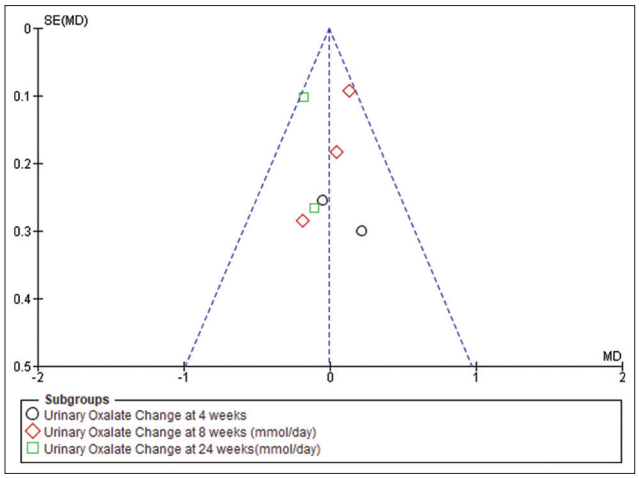

Figure S1: Funnel plot for publication bias in studies reporting changes in urinary oxalate levels

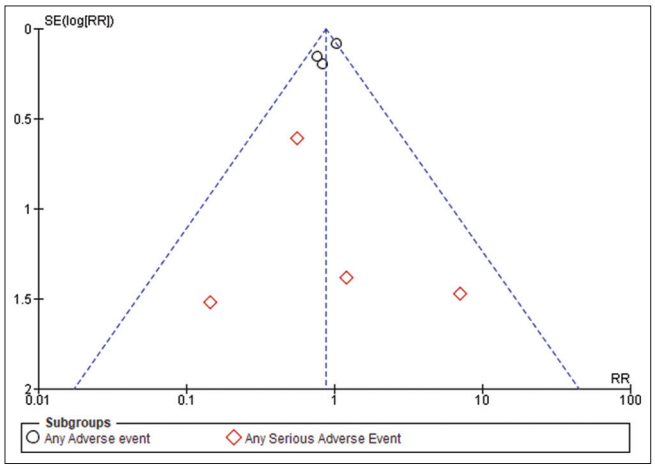

Figure S2: Funnel plot for publication bias in studies reporting safety events

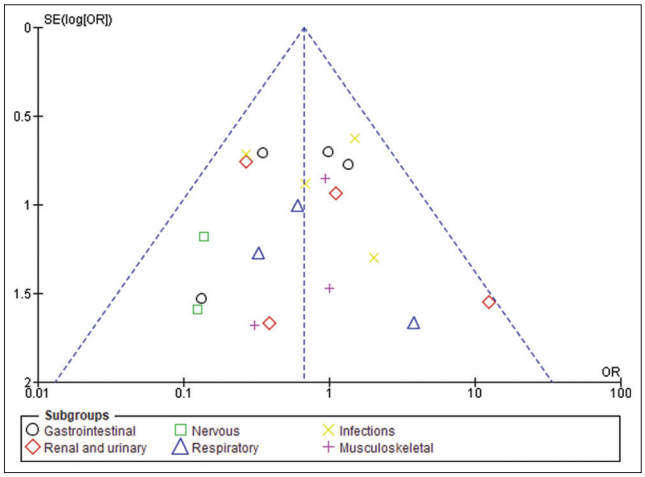

Figure S3: Funnel plot for publication bias in studies reporting systemic adverse events