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EFFECTIVENESS AND SAFETY OF ERDOSTEINIE IN MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): A SYSTEMATIC AND META-ANALYSIS

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Abstract: Effectiveness and Safety of Erdosteine in Management of Chronic Obstructive Pulmonary Disease (COPD: A Systematic and Meta-Analysis. *Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that cause limitation in the airflow and chronic inflammation. Erdosteine has been proposed as a potential therapeutic option for COPD management, based on its antioxidant activity and anti-inflammatory properties. The purpose of this systematic review and meta-analysis is to evaluate the effectiveness and safety of erdosteine in COPD patients. Multiple databases have been involved in the literature study following PRISMA guidelines, identifying randomized controlled trials (RCTs) that compared erdosteine with placebo. A total of seven studies were included in the qualitative analysis, and nine were analyzed quantitatively. Meta-analysis results indicated that erdosteine significantly improved forced expiratory volume in one second (FEV1), reduced reactive oxygen species (ROS) and 8-isoprostan levels, and lowered interleukin-8 (IL-8) concentrations. Subgroup analyses demonstrated greater benefits in patients with moderate to severe COPD (stage II/III). Safety analysis revealed that erdosteine was generally well-tolerated, with only mild adverse effects reported. However, study limitations included high heterogeneity and potential bias in some trials. Overall, the findings suggest that erdosteine is an effective and safe adjunct therapy for COPD.*
Keywords: *COPD, Erdosteine, Management, Meta-Analysis, Rcts*

Abstrak: Efektivitas serta Keamanan Erdosteine dalam Penanganan Penyakit Paru Obstruktif Kronik (PPOK): Tinjauan Sistematis dan Meta-Analisis. Penyakit paru obstruktif kronik (PPOK) merupakan gangguan paru jangka panjang yang ditandai dengan hambatan aliran udara dan peradangan kronis di saluran napas. Erdosteine telah menjadi salah satu kandidat terapi tambahan yang menjanjikan untuk penanganan PPOK, terutama karena kemampuannya sebagai antioksidan dan sifat antiinflamasi yang dimilikinya. Tujuan dari kajian ini adalah untuk menilai secara komprehensif efektivitas dan aspek keamanan penggunaan erdosteine pada pasien dengan PPOK, melalui pendekatan tinjauan sistematis dan meta-analisis. Proses pencarian literatur dilakukan pada berbagai basis data, mengacu pada panduan PRISMA, dan difokuskan pada uji klinis terkontrol secara acak (RCT) yang membandingkan erdosteine dengan plasebo. Sebanyak tujuh penelitian dimasukkan dalam analisis kualitatif, dan sembilan studi dianalisis secara kuantitatif. Hasil meta-analisis menunjukkan bahwa penggunaan erdosteine dapat meningkatkan volume ekspirasi paksa detik pertama (FEV1), serta menurunkan kadar reactive oxygen species (ROS), 8-isoprostan, dan interleukin-8

(IL-8). Analisis subkelompok juga menunjukkan bahwa pasien dengan PPOK stadium sedang hingga berat (stadium II/III) memperoleh manfaat yang lebih nyata. Dari sisi keamanan, erdosteine umumnya dapat ditoleransi dengan baik, dengan efek samping ringan sebagai keluhan yang paling sering dilaporkan. Meskipun demikian, perlu dicatat bahwa terdapat keterbatasan dalam studi-studi yang dianalisis, seperti tingginya variasi data (heterogenitas) dan potensi bias dalam beberapa uji klinis. Secara keseluruhan, temuan ini mendukung penggunaan erdosteine sebagai terapi tambahan yang efektif dan relatif aman dalam pengelolaan PPOK.
Kata Kunci: PPOK, Erdosteine, Penanganan, Meta-Analisis, Uji Terkontrol Acak

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that cause limitation in the airflow and chronic inflammation, resulting in decrease lung function (O'Reilly., 2016). With population growth and urbanisation, COPD significantly impact patient's functional status and quality of life, affecting approximately one in ten individuals and has emerged as one of the three leading cause of death worldwide (Adeloye et al., 2019; Halpin et al., 2019).

Although various strategies have been employed to manage COPD effectively—including efforts aimed at reducing exacerbations, hospitalizations, and readmissions—the incidence of COPD is expected to rise in the coming decades. This is particularly concerning in countries with low-to-middle income economies, high poverty rates, and poor hygiene practices (Calverley et al., 2022; Hillas et al., 2013). This global challenge underscores the critical need to reduce the prevalence of COPD through targeted therapeutic interventions, particularly regarding potential medications such as erdosteine.

Erdosteine is an oral mucoactive agent having anti-inflammatory antioxidant properties. It stimulates the synthesis of GSH (glutathione), which reduces bacterial adhesiveness and enhances the efficacy of antibiotic therapy (Calverley et al., 2019). Furthermore, erdosteine has demonstrated the ability to inhibit several key mediators, including reactive oxygen species (ROS), which plays a crucial role in oxidative stress and inflammation. Collectively, these properties suggests that erdosteine may be beneficial in the management of COPD (Budiono et al., 2019). The use of erdosteine as a potential treatment for COPD is also supported by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Agusti et al., 2023; Papi et al., 2020; Vora et al., 2025).

The potential efficacy of erdosteine warrants further investigation. Previous reports have reviewed its effectiveness in managing COPD (Calverley et al.,2019). Conversely, an insignificant finding between erdosteine and placebo exacerbation frequency and duration was also reported (Dal Negro et al., 2017). These conflicting results emphasize the need for further research through a comprehensive systematic review and meta-analysis to rigorously validate the effectiveness and safety of erdosteine as a potential therapeutic approach for COPD. Consequently, this study aims to evaluate the clinical efficacy and potential adverse effects of erdosteine in the therapeutic management of COPD, synthesizing evidence from a wide array of existing research.

METHOD

Cochrane Handbook for Systematic Reviews of Interventions was used as a guideline to conduct this study, which adheres to the flow diagram of the PRISMA guideline. The analyzed data is sourced from multiple databases based on Randomized Controlled Trial (RCT). Included databases were Cochrane, PubMed, ResearchGate, ScienceDirect, and Google Scholar. The full search strategy was developed using PICOs criteria, with MeSH keywords, such as "erdosteine", "chronic obstructive pulmonary disease", "COPD", "pulmonary disease". No restriction towards date and language of the studies. The complete search keywords are listed in Table 1.

Table 1. Search strategies and keywords used in this study

Source	Keyword
Cochrane	erdosteine AND ("chronic obstructive pulmonary disease" OR COPD)
PubMed	(Erdosteine [Title/Abstract] OR "erdosteine" [Supplementary Concept]) AND ("chronic obstructive pulmonary disease"[Title/Abstract] OR COPD [Title/Abstract] OR "Pulmonary Disease, Chronic Obstructive"[Mesh])
ResearchGate	erdosteine AND ("chronic obstructive pulmonary disease" OR COPD)
ScienceDirect	erdosteine AND ('chronic obstructive pulmonary disease' OR COPD)
Google Scholar	erdosteine AND "chronic obstructive pulmonary disease"|COPD

The searches conducted within these databases employed several filters, including individuals diagnosed with COPD who are 18 years of age or older, studies involving human subjects, including both parents and healthy controls, as relevant to the research, and randomized controlled trial (RCT) study. The data collected from these searches adhered to the inclusion and exclusion criteria, established by the PRISMA guidelines, which ensure the rigor and reliability of systematic review. The inclusion criteria used in our study are summarized in Table 2.

Table 2. Inclusion criteria used in this study

Description	
Patient	COPD patient age ≥18 years old
Intervention	The use of erdosteine as a therapeutic approach in the management of COPD
Comparrison	Placebo
Outcome	
Primary	FEV1 (Forced Expiratory Volume in one second), ROS (Reactive Oxygen Species), 9-isoprostan, or IL-8
Secondary	Frequency and duration of exacerbation, CRP (C-Reactive Protein), GSH (glutathione) concentration, TNF- α (Tumor Necrosis Factor α), BCS (Breathlessness, Cough, and Sputum) scale, hospital stay duration, SGRQ (St. George's Respiratory Questionnaire), FVC (Forced Vital Capacity), FEV25-75%, PEFR (Peak Expiratory Flow Rate), RV (Residual Volume), and the cellular composition of the tracheobronchial tree.

Qualitative analysis

The data were separately extracted two independent reviewers. Qualitative analysis was done according to the CONSORT guideline. The evaluation of quality in relation to the risk of bias for each included study will be conducted qualitatively using the Risk of Bias (RoB) tool.

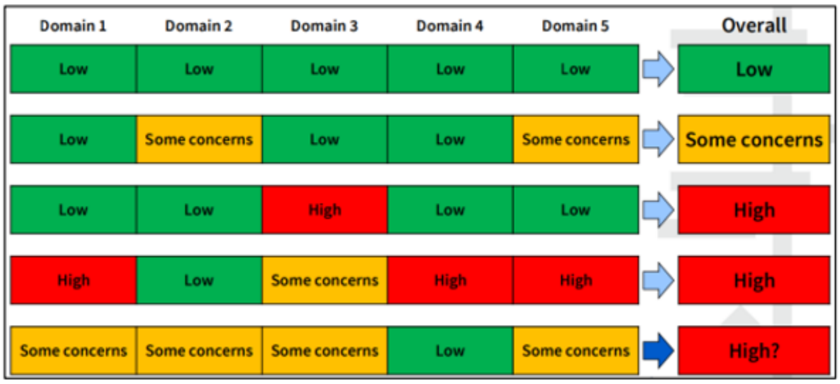

Figure 1. Overall assessment of the risk of bias

Quantitative analysis

All selected studies will be conducted using Review Manager version 5.4. Each identified outcome will be systematically examined, including Manager version 5.4. Each identified outcome will be systematically examined, including FEV1, ROS, 8-isoprostane, IL-8, frequency and duration of exacerbations, CRP levels, GSH concentrations, CAT scores, e-NO, IL-6, TNFα, BCS scale, length of hospital stay, SGRQ, FVC, FEV25-75%, PEFR, RV, and the cellular composition of the tracheobronchial tree.

A random-effects model will be employed if $I^2 \geq 50\%$ and P heterogeneity is <0.05; otherwise, a fixed-effects model will be applied. Statistical significance is determined by an overall effect p-value of <0.05, with a 95% confidence interval (CI) used for estimation.

Sensitivity analysis

Sensitivity analysis evaluates the robustness of study findings by assessing the risk ratios through quantitative analysis. The results are compared between the full dataset and subsets excluding the studies with a high risk of bias using Review Manager version 5.4.

RESULT

Overall, 1001 studies were retrieved through the initial search strategy through Cochrane, Pubmed, ResearchGate, ScienceDirect, and Google Scholar. A total of 27 studies were excluded due to duplication, resulting in 974 screened studies based on title and abstract. From those studies, 963 reports were excluded, with the most common reason for exclusion being the irrelevant topic of study. An overall count of 11 studies were further evaluated, leading to the exclusion of 2 studies due to similar results. Thus, 7 RCT studies were analyzed qualitatively, and 9 RCT studies were analysed quantitatively.

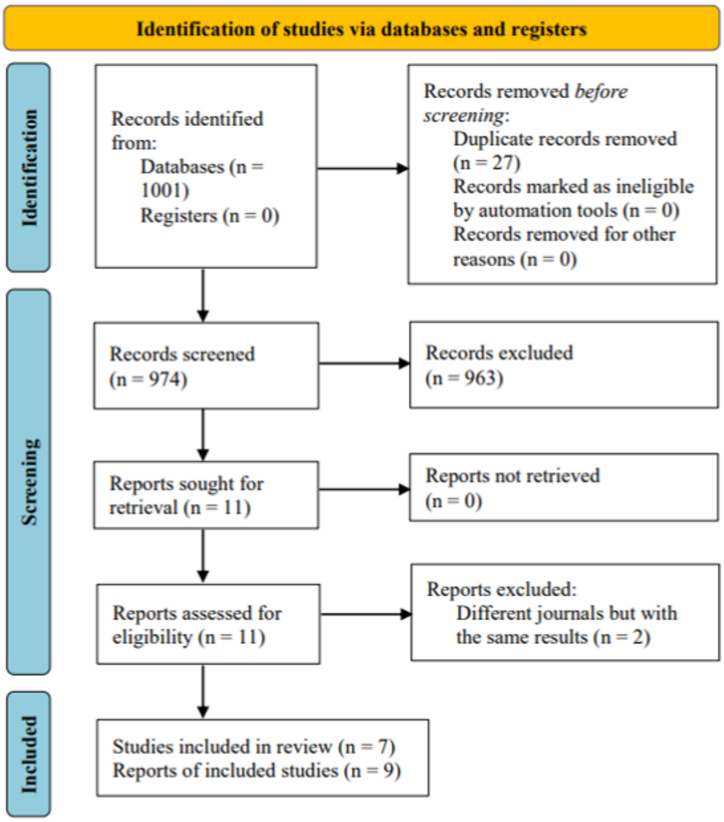

Figure 2. PRISMA flow chart

Qualitative analysis

The qualitative analysis in this study involved seven random controlled trials (RCTs) consisted of adults aged ≥18 years, with sample sizes ranging from 20 to 445 participants. Erdosteine was administered with doses ranging from 600 to 900 mg per day varying from 10 days to 12 months (Budiono et al., 2019; Dal Negro et al., 2017; Puspitasari et al., 2015; Moretti et al.,2015; Dal Negro et al., 2008; Moretti et al., 2004; Kuzhko et al., 2020; Dal Negro et al., 2015; Dal Negro & Visconti., 2016).

Consort checklist

The CONSORT guidelines outline the key aspects needed to be reported, ensuring the comprehensiveness in reporting and reducing the risk of bias in systematic review and meta-analyse. Additionally, the CONSORT guideline aids in the evaluation of the risk of bias (Moher et al., 2010).

Risk of bias

Among the seven studies assessed, Domain 1 (randomization process) showed that 14.3% (1 study) had a low risk of bias, 71.4% (5 studies) raised concerns, and 14.3% (1 study) had a high risk of bias. Meanwhile, Domain 2 (deviations from intended interventions) indicated that 42.9% (3 studies) had a low risk, while 57.1% (4 studies) raised concerns; no studies exhibited a high risk of bias. For domain 3 (missing outcome data), 57.1% (4 studies) had a low risk, none raised concerns, and 42.9% (3 studies) had a high risk of bias. Domain 4 (outcome measurement) revealed 71.4% (5 studies) had a low risk and 28.6% (2 studies) raised concerns, with no studies classified as high risk. Finally, domain 5 (selection of reported outcomes) demonstrated that all studies (100%, 7 studies) had a low risk of bias, with no concerns or high-risk classifications. Overall, across all five domains, 14.3% (1 study) had a low risk of bias, 42.9% (3 studies) raised concerns, and 42.9% (3 studies) had a high risk of bias. The findings for RoB assessment are summarised in Table 3 and Table 4.

Table 3. Risk of bias for each study

Study	D1	D2	D3	D4	D5	Overall
Dal Negro, *et al*., 2017	+	+	+	+	+	+
Budiono, *et al*., 2017	!	+	-	+	+	-
Puspitasari, *et al*., 2015	!	!	+	!	+	!
Dal Negro, *et al*., 2008	!	!	-	+	+	-
Moretti & Fagnani, 2015	!	!	+	+	+	!
Moretti, *et al*., 2004	!	+	+	!	+	!
Kuzhko, *et al*., 2020	-	!	-	+	+	-

\+ Risiko bias rendah

! Terdapat beberapa kekhawatiran terkait risiko bias

\- Risiko bias tinggi

Table 4. Risk of bias percentage

	Randomi-zation Process	Deviations from intended interven-tions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Assignment to intervention (the 'intention-to-treat' effect) Total number of studies = 7						
Low risk.	14.3%	42.9%	57.1%	71.4%	100%	14.3%
Some concerns	71.4%	57.1%	0%	28.6%	0%	42.9%
High risk	14.3%	0%	42.9%	0%	0%	42.9%

GRADEpro

The study was further assessed using GRADEpro, which evaluates the certainty of evidence. Certainty may be downgraded due to some factors, i.e. indirectness, risk of bias, imprecision, inconsistency, and publication bias. The findings from GRADEpro are summarized in Table 5.

Tabel 5. Qualitative analysis based on GRADEpro

Outcomes	Anticipated absolute effect (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with (comparation)	Risk with Erdosteine			
FEV1 score	-	SMD 1.23 SD higher (0.49 higher to 1.97 higher)	-	234 (4 RCTs)	Moderate
ROS level	The mean ROS was 0 FU	MD 78.88 FU lower (113.5 lower to 44.25 lower)	-	68 (3 RCTs)	Moderate
8-isoprotane level	The mean 8-isoprotane was 0 pg/mL	MD 3.85 pg/mL lower (6.01 lower to 1.68 lower)	-	68 (3 RCTs)	Moderate
Il-8 level	The mean IL-8 was 0 pg/mL	MD 13898.99 pg/mL lower (27489.53) lower to 308.46 lower)	-	46 (2 RCTs)	Very low

Quantitative analysis

a) FEV1 score

The analysis of FEV1 values encompassed four studies (Puspitasari et al.,2015; Moretti et al., 2015; Moretti et al., 2004; Kuzhko et al., 2020). A substantial degree of heterogeneity was observed among the studies ($I^2 = 82\%$), necessitating the use of a random-effects model to ensure a more robust and accurate findings. The forest plot result demonstrates that, collectively, these studies provide compelling statistical evidence, supporting the efficacy of erdosteine in significantly improving FEV1 values (SMD = 1.23; 95% CI = 0.49–1.97; p = 0.001). The corresponding forest plot is illustrated in Figure 3.

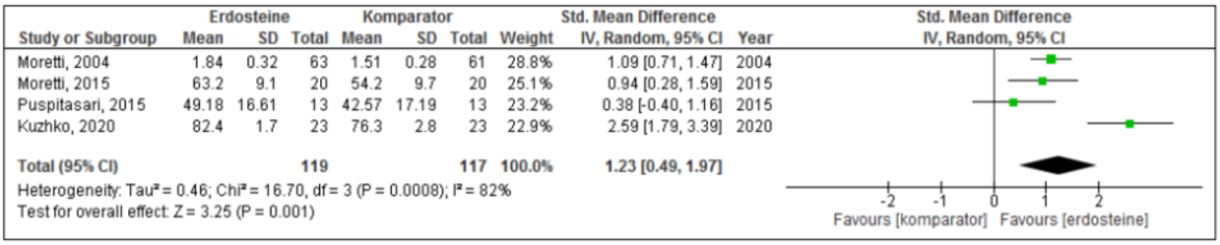

Figure 3. Forest plot depicting the effect of erdosteine on FEV1 score

b) ROS levels

The analysis of ROS levels included 3 studies (Dal Negro et al., 2008; Dal Negro et al., 2015; Dal Negro & Visconti., 2016). Study by Dal Negro, *et al.* reported three separate outcome measures based on intervention days: day 4, day 7, and day 10, while Deng, *et al*. study provided four separate outcome measures, assessing the effects of erdosteing 600 mg and 900 mg at week 2 and week 4 as separate outcomes. A significant level of heterogeneity was observed across studies ($I^2 = 88\%$), necessitating the use of a random-effects model. The forest plot results indicate that erdosteine significantly reduced ROS levels (MD = -78.88; 95% CI = -113.50 to -44.25; $p < 0.00001$). The forest plot is presented in Figure 4.

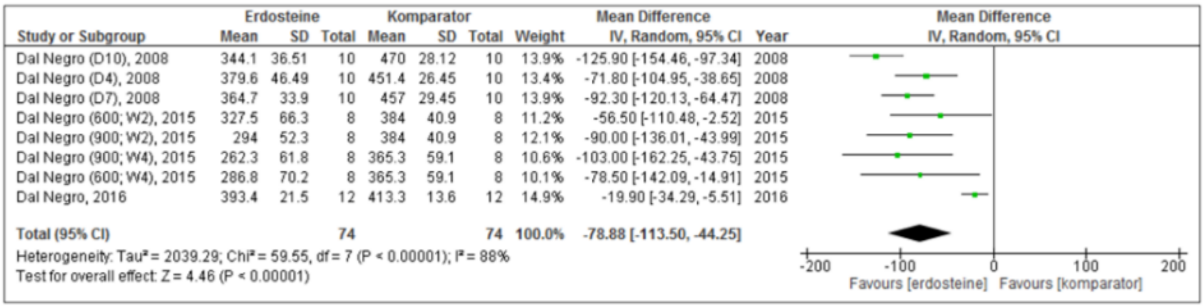

Figure 4. Forest plot illustrating the effect of erdosteine on ROS

c) 8-Isoprostan level

The analysis of 8-isoprostan levels included three studies (Dal Negro et al., 2008; Dal Negro et al., 2015; Dal Negro & Visconti., 2016). Dal Negro, *et al.* reported separate outcomes at day 4, day 7, and day 10. Deng Negro, *et al.* included four separate outcomes: erdosteine 600 mg and 900 mg at week 2 and week 4. Due to significant heterogeneity ($I^2 = 86\%$), a random-effects model was applied. The forest plot demonstrated that erdosteine significantly reduced 8-isoprostane levels (MD = -3.85; 95% CI = -6.01 to -1.68; $p = 0.0005$). The forest plot is shown in Figure 5.

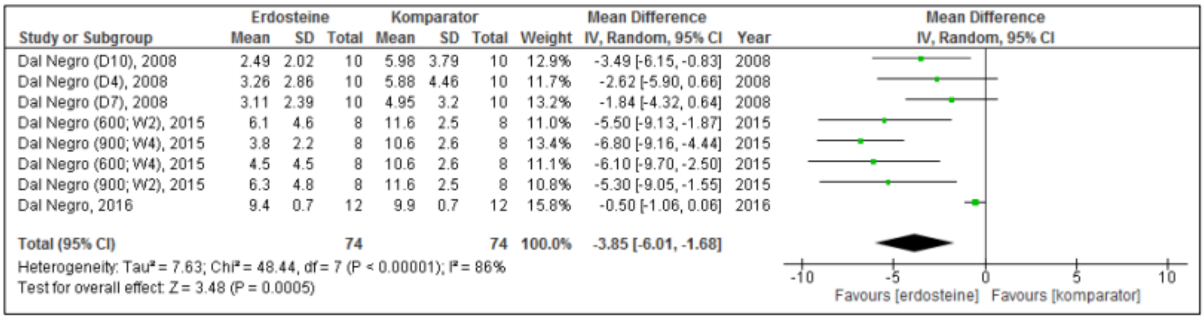

Figure 5. Forest plot on 8-Isoprostan level

Sensitivity analysis

a) FEV1 Score

The sensitivity analysis of FEV1 values included three studies (Puspitasari et al., 2015; Moretti et al., 2015; Moretti et al., 2004). In this analysis, study done by Kuzhko, *et al.* which had a high risk of bias, was excluded. With no significant heterogeneity between studies (I^2 = 23%), a fixed-effects model was applied. The forest plot showed that erdosteine significantly improved FEV1 values (SMD = 0.95; 95% CI = 0.65 to 1.25; $p < 0.00001$). Figure 6 demonstrates the forest plot analysis.

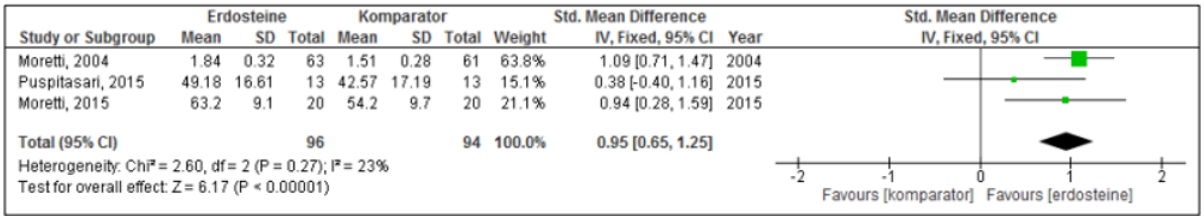

Figure 6. Forest plot sensitivity analysis of FEV1

b) ROS levels

The sensitivity analysis of ROS levels included two studies (Dal Negro et al., 2015; Dal Negro & Visconti., 2016). The study by Dal Negro, *et al.* was excluded due to a high risk of bias (Dal Negro et al., 2008). Dal Negro, *et al.* reported four separate outcomes: erdosteine 600 mg and 900 mg at week 2 and week 4. Due to significant heterogeneity (I^2 = 77%), a random-effects model was applied. The forest plot demonstrated a statistically significant reduction in ROS levels with erdosteine (MD = -65.11; 95% CI = -105.00 to -25.22; p = 0.001). The forest plot is presented in Figure 7.

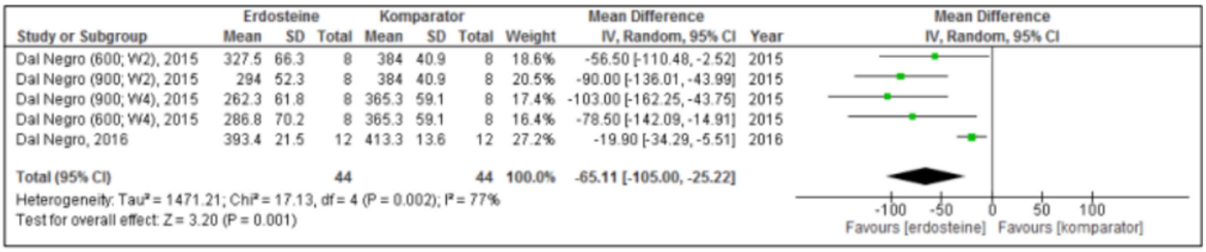

Figure 7. Forest plot sensitivity analysis of ROS level

c) 8-Isoprostan level

The sensitivity analysis of 8-isoprostan levels included two studies (Dal Negro et al., 2015; Dal Negro & Visconti., 2016). The study by Dal Negro *et al*. was excluded due to a high risk of bias (Dal Negro et al., 2008). Dal Negro, *et al* reported four separate outcomes: erdosteine 600 and 900 mg at week 2 and week 4. Due to significant heterogeneity (I^2 = 91%), a random-effects model was applied. The forest plot demonstrated a statistically significant reduction in 8-isoprostan levels with erdosteine (MD = -4.70; 95% CI = -8.25 to -1.14; p = 0.010). The forest plot is presented in Figure 8.

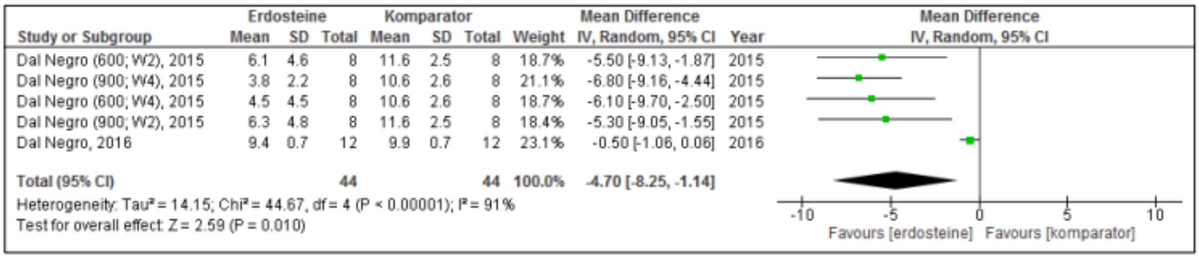

Figure 8. Forest plot sensitivity analysis of 8-Isoprotan level

Subgroup analysis

The subgroup analysis was conducted based on the severity of COPD. Studies included in this analysis were focused on participants with stage II and/or III COPD (moderate and/or severe). The aim of this analysis was to evaluate the effectiveness of erdosteine in improving FEV1 values, reducing ROS levels, and decreasing 8-isoprostan levels in individuals with stage II and/or III COPD.

a) FEV1 value

The subgroup analysis of FEV1 values included three studies (Puspitasari et al., 2015; Moreetti et al., 2004; Kuzhko et al., 2020). Given the low heterogeneity ($I^2 = 24\%$), a fixed-effects model was used. The forest plot demonstrated that erdosteine significantly improved FEV1 values in individuals with COPD stage II and/or III (SMD = 0.97; 95% CI = 0.67 to 1.26; $p < 0.00001$). Figure 9 shows the forest plot.

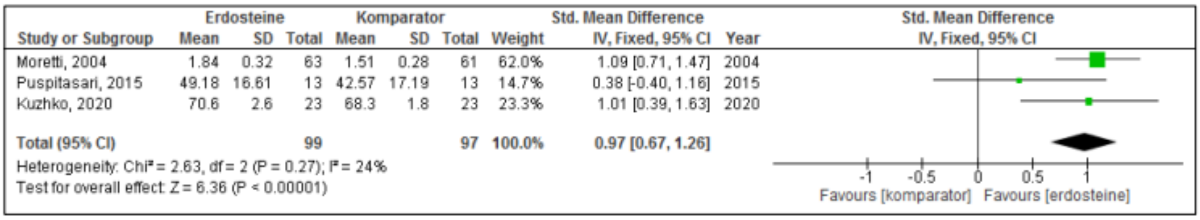

Figure 9. Forest plot subgroup analysis of FEV1 value

b) ROS Level

The subgroup analysis of ROS levels included two studies (Dal Negro et al., 2015; Dal Negro & Visconti., 2016). Dal negro, *et al.* reported four separate outcomes: erdosteine 600 mg and 900 mg at week 2 and week 4. Due to significant heterogeneity ($I^2 = 77\%$), a random-effects model was applied. The forest plot showed that erdosteine significantly reduced ROS levels in individuals with COPD stage II and/or III (MD = -65.11; 95% CI = -105.00 to -25.22; $p = 0.001$). The forest plot is presented in Figure 10.

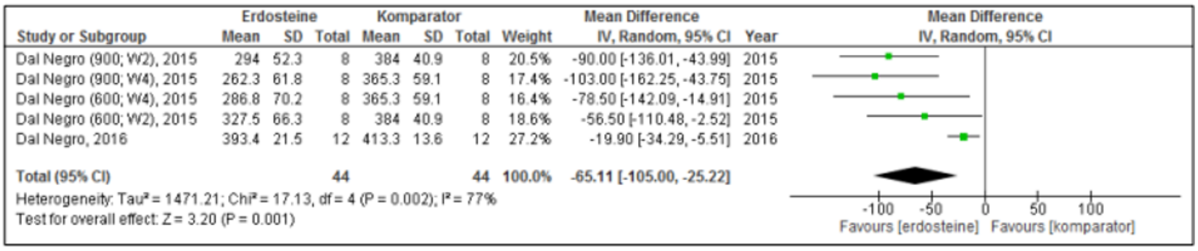

Figure 10. Forest plot subgroup analysis of ROS levels

c) 8-Isoprostan Level

The sensitivity analysis of 8-isoprostan levels included two studies (Dal Negro et al., 2015; Dal Negro & Visconti., 2016). Dal Negro, *et al.* reported four separate outcomes: erdosteine 600 mg and 900 mg at week 2 and week 4. Due to significant heterogeneity (I^2 = 91%), a random-effects model was applied. The forest plot revealed that erdosteine significantly reduced 8-isoprostan levels in individuals with COPD stage II and/or III (MD = -4.70; 95% CI = -8.25 to -1.14; p = 0.010). The forest plot is presented in Figure 11.

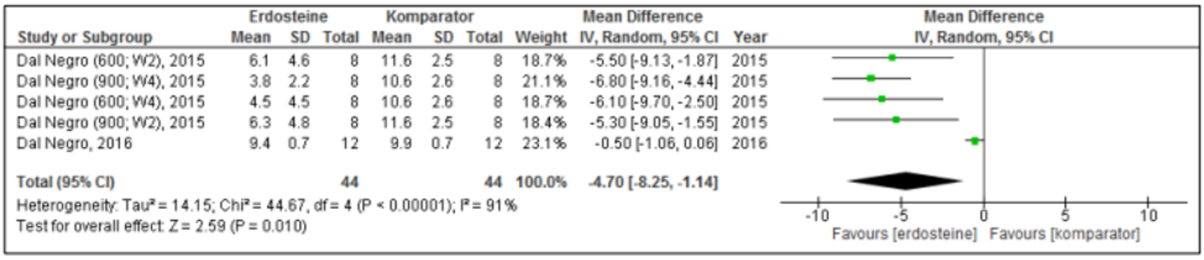

Figure 11. Forest plot subgroup analysis of 8-isoprostan

d) Safety of erdosteine

Based on the studies included, the safety of erdosteine was summarized in Table 6.

Table 6. Safety of erdosteine based on studies

Study	Side Effects
Dal Negro *et al.*, 2017	Atrial fibrilation, gallbladder empyema, abnormal liver function test, gastric ulcer, insomnia, acidosis, and nausea
Budiono *et al.*, 2017	Gastrointestinal, central nervous system (CNS)
Puspitasari *et al.*, 2015	No side effects
Dal Negro *et al.*, 2008	No side effects
Moretti & Fagnani, 2015	No side effects
Moretti *et al.*, 2004	Epigastrium pain, nausea, dyspepsia, headache
Kuzhko *et al.*, 2020	Did not report side effects
Dal Negro *et al.*, 2015	No side effects
Dal Negro & Visconti, 2016	Did not report side effects

DISCUSSION

The qualitative analysis in this study was conducted using the CONSORT guideline, which also informed the quality evaluation through Rob assessment. Based on the CONSORT checklist, the study by Dal Negro, *et al.* met 29 criteria, categorizing its reporting as good (Dal Negro et al., 2017). In contrast, six other studies—Budiono, *et al.*, Puspitasari, *et al.*, Dal Negro, *et al.*, Moretti & Fagnani, Moretti, *et al.*, and Kuzhko, *et al.*—met moderate reporting standards (Budiono et al., 2019; Puspitasari et al., 2015; Moretti et al., 2015; Dal Negro et al., 2008; Moretti et al., 2004; Kuzhko et al., 2020).

The RoB quality assessment for Domain 1, which evaluates the randomization process, identified one study with a low risk of bias (Dal Negro et al., 2017). However, most studies—Budiono, *et al.*, Puspitasari, *et al.*, Dal Negro, *et al.*, Moretti & Fagnani, and Moretti, *et al.*—raised concerns about potential bias, likely due to insufficient details regarding the randomization process and, allocation concealment (Budiono et al., 2019; Puspitasari et al., 2015; Moretti et al., 2015; Dal Negro et al., 2008; Moretti et al., 2004; Kuzhko et al., 2020). Additionally, one study (Kuzhko, *et al.*) was classified as high risk of bias as it lacked detailed information on randomization procedures and did not report baseline characteristics.

Domain 2, assessing deviations from the intended intervention, identified three studies (Dal Negro, *et al.*, Budiono, *et al*., Moretti, *et al.*) with a low risk of bias, while four studies (Puspitasari, *et al.*, Dal Negro, *et al.*, Moretti & Fagnani, Kuzhko, *et al.*) raised concerns (Budiono et al., 2019; Dal Negro et al., 2017; Puspitasari et al., 2015; Moretti et al., 2015; Dal Negro et al., 2008; Moretti et al., 2004; Kuzhko et al., 2020). These concerns stemmed from unclear blinding details and insufficient information on randomization and missing outcome data, limiting the ability to assess the accuracy of the analysis.

Domain 3, assessing missing outcome data, found four studies (Dal Negro, *et al.,* Puspitasari, *et al.,* Moretti & Fagnani; Moretti, *et al.*) with low bias risk, supported by adequate sample sizes and power calculations. (Dal Negro et al., 2017; Puspitasari et al., 2015; Moretti et al., 2015; Moretti et al., 2004). In contrast, three studies (Budiono, *et al.,* Dal Negro*, et al.,* Kuzhko, *et al.*) had high bias risk (Budiono et al., 2019; Dal Negro et al., 2008; Kuzhko et al., 2020). Budiono, *et al.* failed to reach the required sample size, with missing data linked to exacerbations in the erdosteine group, potentially biasing results (Budiono et al., 2019). Dal Negro, *et al.*, and Kuzhko, *et al.* lacked information on power calculations, further increasing bias risk (Dal Negro et al., 2008; Kuzhko et al., 2020).

Domain 4, evaluating outcome measurement, five studies (Dal Negro, *et al.*, Budiono, *et al.*, Dal Negro, *et al*., Moretti & Fagnani, Kuzhko, *et al.*) with low bias risk (Budiono et al., 2019; Dal Negro et al., 2017; Moretti et al., 2015; Dal Negro et al., 2008; Kuzhko et al., 2020). These studies predefined and consistently reported outcomes, with no differences in measurement between intervention groups. Dal Negro, *et al.* ensured blinding for all assessors, while the remaining studies relied on laboratory-based measurements. Conversely, Puspitasari, *et al.* and Moretti, *et al.* raised concerns about bias due to unclear blinding procedures.

Domain 5, assessing the selection of reported outcomes, indicated low risk of bias across all studies (Dal Negro, *et al.,* Budiono, *et al.,* Puspitasari, *et al.,* Dal Negro *et al*., Moretti & Fagnani, Moretti, *et al*., Kuzhko, *et al.*) (Budiono et al., 2019; Dal Negro et al., 2017; Puspitasari et al., 2015; Moretti et al., 2015; Dal Negro et al., 2008; Moretti et al., 2004; Kuzhko et al., 2020). All studies predefined and consistently reported outcomes, with no evidence of selective reporting.

The overall risk of bias assessment revealed that among the seven qualitatively evaluated studies, one study (Dal Negro, *et al.*) had a low risk of bias, three studies (Puspitasari, *et al.,* Moretti & Fagnani, Moretti, *et al.*) raised some concerns, and three studies (Budiono, *et al*., Dal Negro, *et al*., Kuzhko, *et al.*) had a high risk of bias (Budiono et al., 2019; Dal Negro et al., 2017; Puspitasari et al., 2015; Moretti et al., 2015; Dal Negro et al., 2008; Moretti et al., 2004; Kuzhko et al., 2020). This indicates that most studies were of limited quality, with biases in randomization, intervention deviations, missing outcome data, and outcome measurements. The GRADEpro yielded similar results, categorizing the overall study quality as very low to moderate.

The assessment using the CONSORT checklist and RoB 2 showed consistency in Dal Negro, *et al.*, which met good reporting criteria and had a low risk of bias (Dal Negro et al., 2017). Similarly, Puspitasari, *et al.*, Moretti & Fagnani, and Moretti, *et al*. met moderate reporting criteria and raised some concerns regarding bias (Puspitasari et al., 2015; Moretti et al., 2015; Moretti et al., 2004). However, Budiono, *et al.*, Dal Negro, *et al.*, and Kuzhko, *et al.* were rated as having moderate reporting quality based on the CONSORT checklist, yet exhibited a high risk of bias according to RoB (Budiono et al., 2019; Dal Negro et al., 2008; Kuzhko et al., 2020). This discrepancy likely arises from differences in evaluation criteria between the CONSORT checklist and RoB, leading to variations in scoring and assessment outcomes.

A similar systematic review by Cazzola, *et al.* analyzed 15 RCTs involving 1,046 patients with chronic bronchitis treated with erdosteine (Cazzola et al., 2010). Study quality was assessed using the Jadad scale, which indicated that most studies were of high quality. However, the Jadad scale primarily evaluates study quality based on randomization, blinding, and dropout reporting, without assessing other potential sources of bias.

Quantitative analysis was performed using Revman version 5.4. The outcomes analysed quantitatively included FEV1, ROS levels, 8-isoprostane levels, and IL-8 levels. Other outcomes, such as exacerbation frequency and duration, CRP levels, GSH levels, CAT scores, e-NO, IL-6, TNFα, BCS scale, hospitalization days, SGRQ, FVC, FEV25-75%, PEFR, RV, and cellular composition of the tracheobronchial tree, were not included in the quantitative analysis due to insufficient study numbers.

The analysis of FEV1 involved four studies: Moretti, *et al.*, Moretti & Fagnani, Puspitasari*, et al.*, and Kuzhko, *et al* (Puspitasari et al., 2015; Moretti et al., 2015; Moretti et al., 2004; Kuzhko et al., 2020). The meta-analysis indicated a significant increase in FEV1 by 1.23 in COPD patients receiving erdosteine compared to the control group. An SMD increase greater than 0.8 represents a large effect size, suggesting clinical significance. However, individual study results varied. Moretti, *et al* reported no significant change in FEV1 after 8 months of erdosteine treatment (Moretti et al., 2004). Similarly, Puspitasari, *et al.* found increased FEV1 in the erdosteine group but no significant difference compared to the placebo, possibly due to the severe stage of COPD stages among participants (Puspitasari et al., 2015). In contrast, Moretti & Fagnani, and Kuzhko, *et al.* both found significant improvements in FEV1 following erdosteine treatment, likely attributed to its mucolytic and antioxidant properties (Moretti et al., 2015; Kuzhko et al., 2020).

The analysis of ROS and 8-isoprostan involved three studies: Dal Negro *et al.*, Dal Negro *et al.*, and Dal Negro & Visconti (Dal Negro et al., 2008; Dal Negro et al., 2015; Dal Negro & Visconti., 2016). Meta-analysis results showed that erdosteine and 8-isoprostan significantly reduced ROS in COPD patients, indicating clinical significance. Dal Negro, *et al*, observed a significant lowering of ROS as early as day 4 and a 10-day treatment (Dal Negro et al., 2008). The slower reduction of 8-isoprostan is attributed to the oxidative process, which takes longer and is slower compared to other pro-inflammatory mediators like ROS. Dal Negro, *et al.*, found that erdosteine reduced both ROS and 8-isoprostan significantly, with a higher dose of 900 mg showing a greater reduction than 600 mg, indicating a dose-dependent effect (Dal Negro et al., 2015). Similarly, Dal Negro & Visconti, demonstrated that erdosteine significantly reduced ROS and 8-isoprostan post exercise, confirming its effectiveness in reducing exercise-induced oxidative stress (Dal Negro & Visconti., 2016).

The analysis of IL-8 levels involved two studies: Dal Negro, *et al.*, and Puspitasari, *et al* (Puspitasari et al., 2015; Dal Negro et al., 2008). Meta-analysis results revealed a significant difference in IL-8 levels between the erdosteine and placebo groups, with erdosteine showing a significant reduction. This decrease in IL-8 is considered clinically significant. Dal Negro, *et al.* demonstrated that erdosteine significantly reduced IL-8 starting from day 4 of a 10-day treatment (Dal Negro et al., 2008). However, Puspitasari *et al.* showed a reduction in IL-8, with erdosteine, but it was not statistically significant, likely due to uncontrolled factors such as cigarette smoke and pollutants during the treatment period.

In this study, sensitivity analysis was performed to determine the robustness of the study results. The analysis showed that excluding high-bias-risk studies did not affect the significance of the outcomes for FEV1, ROS, and 8-isoprostan levels. Sensitivity analysis for IL-8 levels was not performed due to an insufficient number of studies; excluding the high-bias-risk study by Dal Negro, *et al.* would leave only one study, Puspitasari, *et al.* making meta-analysis unfeasible (Puspitasari et al., 2015; Dal Negro et al., 2008).

The findings of this study are consistent with similar research. A meta-analysis by Cazzola, *et al (*Cazzola et al., 2010). demonstrated that erdosteine significantly improved symptoms in chronic bronchitis patients, positively affecting cough frequency, sputum viscosity, and mucus clearance, leading to improved airflow. Another meta-analysis by Cazzola, et al. (Cazzola et al., 2018) also showed that erdosteine was effective in chronic bronchitis and COPD patients, with a longer time to the first exacerbation compared to the control group.

Regarding the safety of erdosteine, a study by Dal Negro, *et al.* reported one serious adverse event (atrial fibrillation) in the erdosteine group and one case of gallbladder empyema in the placebo group (Dal Negro et al., 2017; Rogliani et al., 2019). Additionally, there were two non-serious adverse events (abnormal liver function and gastric ulcer) in the erdosteine group, and four non-serious events (abnormal liver function, insomnia, acidosis, and nausea) in the placebo group. Budiono, *et al.* also identified two gastrointestinal side effects in the erdosteine group and two events (CNS and gastrointestinal) in the placebo group (Budiono et al., 2019). Moretti, *et al.* reported 14 adverse events in the erdosteine group and 19 in the placebo group, with the most common being epigastric pain, nausea, dyspepsia, and headache (Moretti et al., 2004). Studies by Puspitasari*, et al.*, Dal Negro *et al.*, and Kuzhko, *et al.* reported good tolerance to erdosteine, with no adverse events during the study periods (Puspitasari et al., 2015; Dal Negro et al., 2008; Kuzhko et al., 2020). Meanwhile, Kuzhko, *et al.* and Dal Negro & Visconti did not report any adverse events (Kuzhko et al., 2020; Dal Negro & Visconti., 2016). A similar meta-analysis by Cazzola, *et al.* concluded that erdosteine was well-tolerated in patients with chronic obstructive bronchitis, with common side effects including nausea, epigastric pain, and diarrhea (Cazzola et al., 2010).

This study has several limitations, including small number of the studies included. RCT studies on erdosteine as a treatment for COPD are severely limited, and only freely accessible articles were included. However, the researchers made every effort to conduct a thorough search and study selection. The heterogeneity of the results is also quite high; to address this, subgroup analyses were performed, although heterogeneity in the outcomes of ROS and 8-Isoprostan remained significant. Additionally, some studies did not meet power calculations due to small sample sizes, and most studies lacked information on sample sizes and randomization processes, which reduced their quality.

CONCLUSION

This systematic review and meta-analysis conclude that erdosteine is an effective therapeutic agent for COPD. It significantly improves FEV1 values, reduces reactive oxygen species (ROS) levels, and lowers concentrations of 8-isoprostan and interleukin-8 (IL-8). Subgroup analyses indicate greater efficacy in patients with advanced stages of COPD (stages II and III). Erdosteine is generally well-tolerated, with adverse effects being infrequent and mostly mild.

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