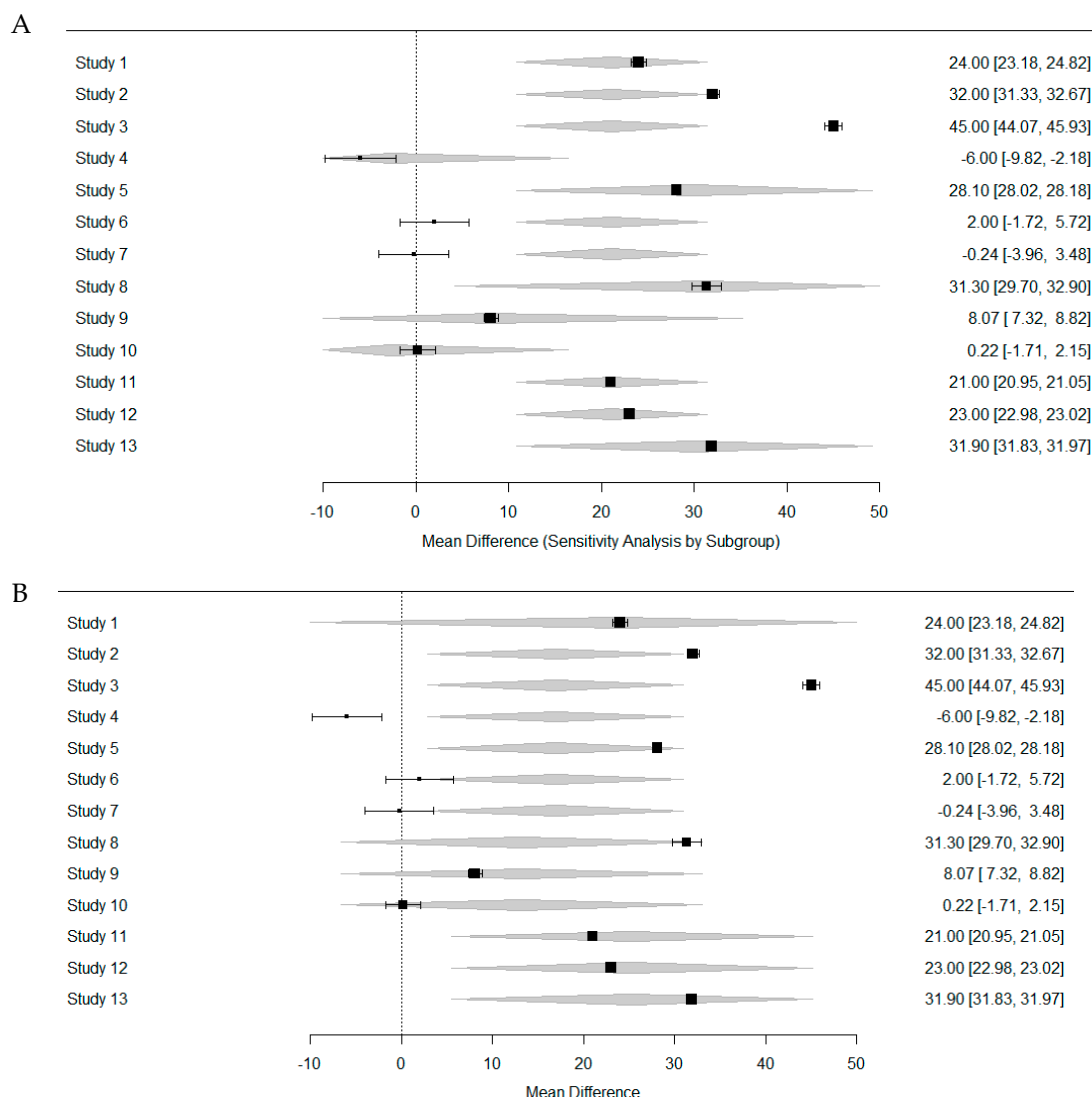
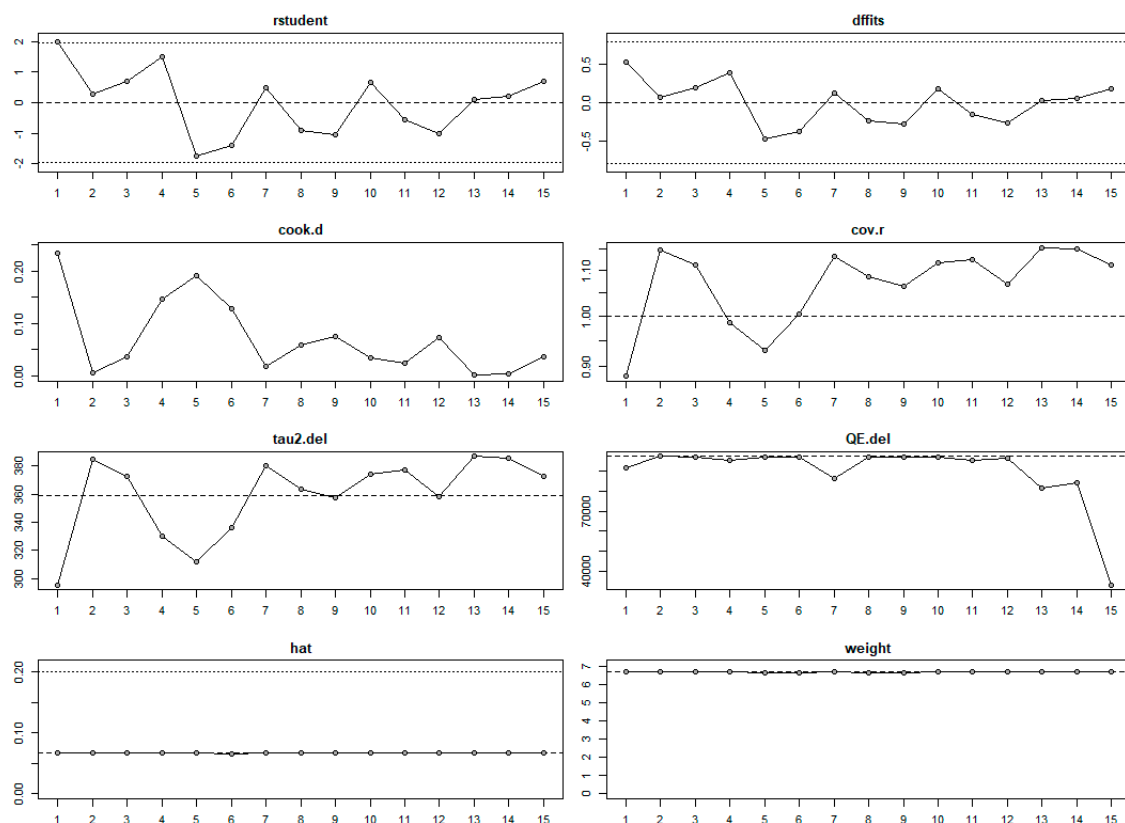


Supplementary Materials:



**Figure S1.** Sensitivity analyses for chronic venous insufficiency interventions. (a) Mixed-effects meta-analysis stratified by intervention types (Coumarin + Troxerutin, Hydroxyethylrutoside, Pycnogenol, and Venoruton). The x-axis shows the mean difference (MD) with 95% confidence intervals, and the y-axis lists data points corresponding to various interventions. The analysis reveals persistent residual heterogeneity ( $\tau^2 = 190.70$ ;  $I^2 = 100\%$ ), with no statistically significant differences among subgroups (QM = 7.78,  $p = 0.0999$ ). (b) Mixed-effects meta-analysis stratified by clinical manifestations (Pain, Quality of Life, and Resting Flux). The x-axis shows the MD with 95% confidence intervals, and the y-axis lists data points corresponding to different manifestations. The analysis indicates no significant moderating effect of clinical manifestations on heterogeneity ( $R^2 = 0.00\%$ ; QM = 0.88,  $p = 0.8313$ ), with residual heterogeneity remaining high ( $\tau^2 = 306.11$ ;  $I^2 = 100\%$ ).



**Figure S2.** Influence analysis of the included studies evaluating the impact of individual studies on the overall meta-analytic results. Metrics such as residual studentized values (rstudent), DFFITS, Cook's distance (Cook.D), variance estimates ( $\tau^2$ ), and heterogeneity statistics (QE) were used to assess the influence of each study. The studies are numbered as follows: 1 (Cesarone et al., 2005; pain; Hydroxyethylrutoside), 2 (Cesarone et al., 2006; pain; Pycnogenol), 3 (Cesarone et al., 2006; edema; Pycnogenol), 4 (Cesarone et al., 2006; edema; Pycnogenol), 5 (Belczak et al., 2013; edema; Aminaphthone), 6 (Belczak et al., 2013; edema; Coumarin + Troxerutin), 7 (Cesarone et al., 2005; edema; Hydroxyethylrutoside), 8 (Toledo et al., 2017; edema; Pycnogenol), 9 (Toledo et al., 2017; edema; Pycnogenol), 10 (Cesarone et al., 2006; quality of life; Venoruton), 11 (Belczak et al., 2013; quality of life; Aminaphthone), 12 (Belczak et al., 2013; quality of life; Coumarin + Troxerutin), 13 (Cesarone et al., 2006; resting flux; Pycnogenol), 14 (Cesarone et al., 2006; resting flux; Pycnogenol), and 15 (Cesarone et al., 2005; resting flux; Hydroxyethylrutoside). This analysis highlights studies with significant influence on the pooled effect size and heterogeneity, providing insights into their contribution to the overall meta-analytic conclusions.

**Table S1.** Search Strategies Used for Bibliographic Databases in the Systematic Review.

DATA BASE	STRATEGY FOR SEARCHING
Medline / PubMed	(((((Venous Insufficiency[Title/Abstract]) OR (Insufficiencies, Venous[Title/Abstract])) OR (Insufficiency, Venous[Title/Abstract])) OR (Venous Insufficiencies[Title/Abstract])) AND ((((((Diosmin[Title/Abstract]) OR (Barosmin[Title/Abstract])) OR (Buchu Resin[Title/Abstract])) OR (Resin, Buchu[Title/Abstract])) OR (Venosmine[Title/Abstract])) OR (Daflon[Title/Abstract])) AND (((((((Hesperidin[Title/Abstract]) OR (Hesperetin 7-Rhamnoglucoside[Title/Abstract])) OR (7-Rhamnoglucoside, Hesperetin[Title/Abstract])) OR (Hesperetin 7 Rhamnoglucoside[Title/Abstract])) OR (Hesperetin-7-Rutinoside[Title/Abstract])) OR (Hesperetin 7 Rutinoside[Title/Abstract])) OR (Hesperidin 2S[Title/Abstract])) OR (2S, Hesperidin[Title/Abstract])) OR (4H-1- Benzopyran-4-one, 7-((6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl)oxy)-2,3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-, (S)-[Title/Abstract])).
Cochrane library and Embase	"venous insufficiency" in Title Abstract Keyword AND "diosmin" in Title Abstract Keyword AND "hesperidin" in Title Abstract Keyword - with Publication Year from 2000 to 2023, in Trials (Word variations have been searched).
Google Scholar	("Venous Insufficiency" OR "Insufficiencies, Venous" OR "Insufficiency, Venous" OR "Venous Insufficiencies") AND ("Diosmin" OR "Barosmin" OR "Buchu Resin" OR "Resin, Buchu" OR "Venosmine" OR "Daflon") AND ("Hesperidin" OR "Hesperetin 7-Rhamnoglucoside" OR "Hesperetin-7-Rutinoside" OR "Hesperidin 2S" OR "4H-1-Benzopyran-4-one, 7-((6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl)oxy)-2,3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-, (S)")
Scopus	TITLE-ABS("venous insufficiency" OR "insufficiencies, venous" OR "insufficiency, venous" OR "venous insufficiencies") AND TITLE-ABS("diosmin" OR "barosmin" OR "buchu resin" OR "resin, buchu" OR "venosmine" OR "daflon") AND TITLE-ABS("hesperidin" OR "hesperetin 7-rhamnoglucoside" OR "7-rhamnoglucoside, hesperetin" OR "hesperetin 7 rhamnoglucoside" OR "hesperetin-7-rutinoside" OR "hesperidin 2S" OR "4H-1-benzopyran-4-one, 7-((6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl)oxy)-2,3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-, (S)")
Web of Science	((ALL=("venous insufficiency")) AND ALL=("diosmin")) AND ALL=("hesperidin")