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Systematic Review

Preclinical Therapeutic Potential of *Peristrophe roxburghiana*: A Systematic Review and Meta-Analysis

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Abstract

This systematic review and meta-analysis assessed the preclinical therapeutic potential of *Peristrophe roxburghiana* extracts (PREs). Among the 46 screened articles, 12 met the inclusion criteria and were quantitatively analyzed. The pooled standardized mean differences (SMDs) between the PRE treatment and control groups were calculated to investigate the antioxidant, biocompatible, anticancer, and antihypertensive effects. PRE exhibited measurable antioxidant activity, with low pooled IC_{50} values for DPPH (3.57 [0.96; 13.34] µg/mL), ABTS (91.96 [47.30; 178.78] µg/mL), and FRAP (63.39 [0.29; 13,992] µmol Fe^{2+}/g extract). Biocompatibility analyses did not indicate a statistically significant reduction in the viability of normal cell lines. By contrast, the PRE treatment was associated with reduced cell viability in cancer cells (SMD = 2.28 [0.54, 4.03], I^2 = 63%). PRE treatment effectively improved the pathological outcomes in L-NAME-induced hypertensive rat models, including reductions in blood pressure parameters and favorable modulation of oxidative stress-related biomarkers. Although several comparisons showed substantial heterogeneity, subgroup and meta-regression analyses identified differences in the methodological approaches (extraction methods, raw materials, and geographical regions) as major contributors. Overall, these findings support the preclinical therapeutic potential of PREs and provide a scientific basis for future mechanistic and clinical studies.

Keywords: *Peristrophe roxburghiana*; antioxidant; biocompatibility; anticancer; antihypertensive

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1. Introduction

The use of herbal extracts for therapeutic and daily applications has gained increasing attention in recent years [1–4]. Among these, *Peristrophe roxburghiana* (Schult.) Bremek. (*P. roxburghiana*) is a promising species belonging to the Acanthaceae family and is predominantly distributed across Asia and Africa [4–6]. Taxonomically, *P. roxburghiana* is currently recognized as a synonym of *Peristrophe bivalvis* (L.) Merr., according to authoritative botanical databases, including World Flora Online and Plants of the World Online (Royal Botanic Gardens, Kew) [7,8]. The plant is characterized by opposite ovate leaves, slender stems, and distinctive purplish to magenta tubular flowers arranged in axillary clusters [7,8]. *P. roxburghiana* has been widely utilized as a natural food colorant and medicinal plant (e.g., for blood health, inflammation, and skin ailment treatments) [9–11]. In particular, its leaves yield a strong magenta pigment that is widely used to color rice, cakes, soups, and

desserts, particularly in Southeast Asian cuisines [4,11]. As a medicinal agent, *P. roxburghiana* has been used for detoxification, enhanced blood circulation, reduced inflammation, and the treatment of skin-related ailments [4]. Moreover, *P. roxburghiana* extracts (PREs) have attracted attention in cosmetic and nutraceutical research owing to their anti-aging properties, including anti-glycation and anti-lipid peroxidation, which support skin health and protection [12–15]. In addition to biomedical applications, the leaf extract provides a natural red dye for cotton fabrics, with mordants enhancing the color strength [12,16,17]. Modern research has explored its antioxidant effect, biocompatibility, anti-glycation, and potential cosmetic applications, owing to its rich bioactive compounds.

P. roxburghia contains a variety of bioactive compounds, including phenolics, flavonoids, anthocyanins, tannins, alkaloids, and polysaccharides [4,18–20]. These phytochemicals have been widely investigated in preclinical studies, where they have demonstrated antioxidant, anti-inflammatory, anticancer, and antihypertensive properties in various experimental models [4,20–23]. In particular, plant-derived phenolic compounds and polysaccharides have been reported to exert biological effects through mechanisms such as free radical scavenging, chelation of redox-active metal ions, modulation of oxidative stress-related biomarkers, and regulation of cellular signaling pathways involved in apoptosis, inflammation, and vascular function [4,20–23]. However, the therapeutic implications of these activities remain primarily supported by in vitro and in vivo evidence.

The therapeutic potential of PRE has been increasingly documented, both in vitro and in vivo. For instance, one study evaluated the antioxidant activity of an ethanolic extract of *P. roxburghiana* leaves and reported strong radical-scavenging and reducing capacities [9]. The PRE exhibited a strong 2,2-diphenyl-1-picryhydrazyl (DPPH) radical-scavenging effect (IC_{50} = 136.10 ± 2.69 μg/mL), 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS)-scavenging effects (IC_{50} = 215.85 ± 0.78 μg/mL), and also Ferric reducing antioxidant power (FRAP) activity (IC_{50} = 41.48 ± 0.81 μmol Fe^{2+}/g extract) [9]. Another study reported a higher antioxidant potency when cold-water extraction techniques were employed. A markedly lower DPPH IC_{50} value of 9.91 ± 1.18 μg/mL was obtained, and a total antioxidant capacity IC_{50} of 87.3 ± 0.82 mg ascorbic acid equivalents (AAE)/g extract was observed [24]. These results highlight the multimodal antioxidant properties of PRE and emphasize the influence of the extraction methodology on bioactivity.

The biocompatibility of PRE has been examined using normal human fibroblasts (WS-1) and Vero cells [9,25]. PRE showed negligible cytotoxicity, with a cell viability of approximately 86–101%. By contrast, PRE showed significant antiproliferative effects against human cancer cells (Caco-2, HepG2, Hep-2, A549, and RAW264.7 cells), with reported cell survival rates ranging from 61.5–85.68% [25–27]. Mechanistic analyses suggested that these anticancer effects were mediated through the upregulation of pro-apoptotic signaling pathways, including increased expression of apoptotic mediators (Bax, caspase-9, and caspase-3), thereby supporting an apoptosis-driven mechanism of cancer cell death.

The beneficial effects of PRE on hypertension treatments have been investigated via in vivo studies [14,24,28,29]. In an L-NAME-induced hypertensive rat model, the oral administration of PRE showed a clear blood pressure-lowering effect. Compared with the positive control group, PRE treatment decreased systolic blood pressure (SBP) from 181.7 ± 5.3 to 154.5 ± 4.7 mmHg, diastolic blood pressure (DBP) from 116.3 ± 3.8 to 98.3 ± 2.8 mmHg, and mean arterial pressure (MAP) from 138.1 ± 3.6 to 117.0 ± 3.1 mmHg [24]. These studies revealed that PRE exhibits a combined redox-modulating capacity, cardiovascular benefits in hypertensive models, and a generally favorable biocompatibility profile, while also exhibiting cytotoxic/anti-proliferative activity in cancer cells. This distinctive combination of biological activities is consistent with therapeutic selectivity and underscores the need for a systematic synthesis and meta-analysis evaluation of the available evidence.

Although the biomedical applications of PRE have attracted increased attention, no systematic reviews have yet been published on this compelling topic. Therefore, this study aims to systematically review and quantitatively synthesize the available evidence on the antioxidant, anticancer, antihypertensive, and biocompatibility effects of PRE (Figure 1). By integrating diverse articles using meta-analysis and meta-regression approaches, this study intends to provide an evidence-based assessment of their therapeutic potential, identify sources of heterogeneity, and support future translational and clinical investigations.

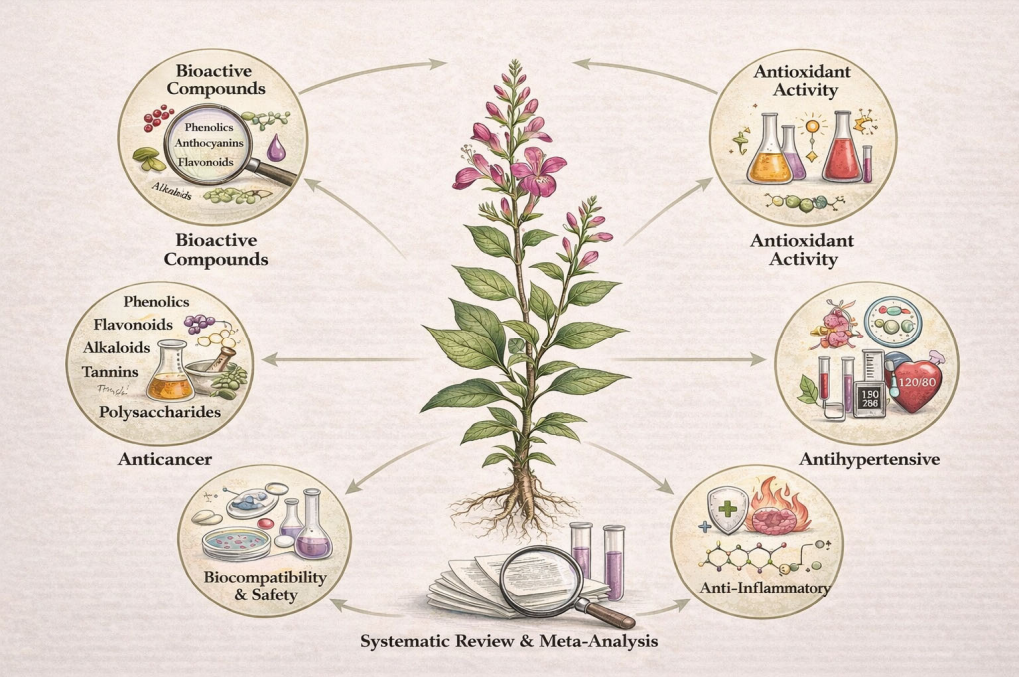


Figure 1. Graphical overview of the preclinical therapeutic potential and reported biological activities of *Peristrophe roxburghiana* extracts (PREs), as synthesized through systematic review and meta-analysis.

2. Materials and Methods

2.1. Literature Search Strategy

This study was designed according to the guidelines of the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) 2020 protocol [30]. A literature search for the therapeutic potential of PRE was conducted between November 2025 and January 2026 using major electronic databases (PubMed, Cochrane, Elsevier, EMBASE, and MedRxiv) (Supplementary Table S1). According to the taxonomic synonym of *P. roxburghiana* and *P. bivalvis*, studies referring to either name are considered to investigate the same biological species and were included in this systematic review. The literature search was performed using the following keywords: *P. roxburghiana*, *P. bivalvis*, therapeutic, antioxidant, anticancer, antihypertensive, biocompatibility, and cell viability. This systematic review has been registered on PROSPERO under the registration number CRD420261283495.

2.2. Study Selection and Data Extraction

2.2.1. Eligibility Criteria and Study Identification

This systematic review included preclinical investigations evaluating the biological activities of PRE. Both in vitro and in vivo studies were considered if they assessed at least one of the following therapeutic domains: antioxidant, anticancer, antihypertensive, or biocompatibility effects. Studies with multiple experimental objectives were selected only

if they directly compared the PRE treatment and control groups. The primary outcomes were reported as the mean ± standard deviation (SD).

Publications investigating additional objectives (e.g., food coloring, pigment extraction, or textile applications) were included a priori. However, only biological outcome data (outcomes (e.g., antioxidant activity, cytotoxicity, or biocompatibility) relevant to the predefined therapeutic endpoints were extracted for analysis.

No limitations were imposed regarding plant part used, extraction solvent or methods, study design, and geographical origin. However, only articles published in English were included in this review.

This study did not include reviews, conference abstracts, primary manuscripts, or seminar presentations.

2.2.2. Data Extraction

Data extraction was conducted independently by two reviewers using a standardized form. Any discrepancies were resolved through discussion until consensus was achieved. The following information was collected: the first author's name, geographical region, year of publication, extraction method, raw material parts (leaves, stems, roots, and branches), physicochemical properties, and biological endpoints (antioxidant, anticancer, antihypertensive, and biocompatibility). The continuous outcomes are presented as the mean ± SD values. When necessary, additional calculations were performed to obtain compatible statistical parameters.

2.3. Statistical Analysis and Meta-Analysis

For all continuous outcomes, pooled effect sizes were calculated as standardized mean differences (SMDs) with a 95% confidence interval (CI) [25]. A random–effects model was applied to account for between-study variability. Statistical significance was defined at the 5% level ($p < 0.05$), and a pooled effect was considered significant when the 95% CI did not include zero. The SMDs were interpreted according to conventional benchmarks: small (SMD $\leq$ 0.2), moderate (SMD ~ 0.5), and large (SMD $\geq$ 0.8) [1,2,31]. Statistical heterogeneity was quantified using the I^2 statistic, with values $\leq$ 25%, approximately 25–50%, or $\geq$50% indicating low, moderate, and high heterogeneity, respectively [1,31].

A meta-analysis of antioxidant activities (DPPH, ABTS, and FRAP scavenging) was performed using IC_{50} values. As IC_{50} values are typically right skewed and multiplicative, all IC_{50} data were analyzed on a log scale [32,33]. Standard errors (SEs) were calculated using the delta method ($SE_{ln(IC50)} = SE/IC_{50}$) [34,35]. Pooled estimates were obtained using a random-effects model with a restricted maximum likelihood (REML) estimation of between-study variance (τ^2) [34]. Hartung–Knapp–Sidik–Jonkman adjusted CIs were calculated for the pooled effect, and the results were back-transformed to report the geometric mean IC_{50} values [36]. According to the literature, antioxidant activity is considered very powerful if pooled IC_{50} values are $\leq$50 µg/mL, strong if IC_{50} falls within 50–100 µg/mL, moderate if IC_{50} values are 101–250 µg/mL, weak when IC_{50} values are 250–500 µg/mL, and inactive if IC_{50} values are $\geq$500 µg/mL [18,19,37].

Where appropriate, subgroup analyses were conducted to explore differences according to methodological characteristics (e.g., extraction method, plant part, or assay type). Publication bias was visually evaluated using funnel plots.

Meta-regression analysis was conducted to explore the source of heterogeneity of the comparisons. In this analysis, SEs were derived from the reported 95% CI. Mixed-effects meta-regression models were fitted using REML.

All analyses were performed using Review Manager (version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and appropriate statistical software for advanced modeling [38].

2.4. Quality Assessment of Included Studies

Because the included studies were in vitro and in vivo experiments rather than randomized controlled trials, conventional clinical risk-of-bias tools were not applicable. Therefore, the methodological quality of the included studies was evaluated using an adapted quality assessment checklist based on previously published approaches for research [39–41].

The checklist consisted of nine items covering experimental design, reproducibility, and reporting transparency, including a description of the test system, sample preparation, use of appropriate controls, replication, concentration range, assay validity, statistical analysis, data reporting, and declaration of conflicts of interest. Each item was scored as "yes" (1 point) or "no/unclear" (0 points), yielding a maximum score of 9 [39–41].

Specifically, the test system was rated as "yes" when the cell line/assay models were clearly described. Sample preparation was based on the thoroughness of the reported extraction method, solvent, and conditions. The domains of the controls were assessed for the inclusion of appropriate positive and negative controls. Replication received a positive score when the experiments were performed in triplicate or more. Multiple concentrations and dose–response relationships were examined. The validity of the assay was confirmed using various methods (e.g., DPPH, ABTS, FRAP, and MTT assays). The statistical analysis domain was evaluated based on the presentation of results as the mean ± SD/SE. Data clarity refers to the availability of sufficient numerical data for extraction. Transparency was evaluated based on an explicit statement or clear absence of any conflicts of interest.

Studies scoring 6–9 points were classified as high quality, those scoring 5–6 points as moderate quality, and those scoring 4 points or fewer as low quality. Quality assessment was conducted independently by two reviewers and discrepancies were resolved through discussion.

3. Results

3.1. Characteristics of Included Studies

The screening process for eligible studies is shown in the flowchart (Figure 2). A total of 46 publications were identified by searching electronic databases using the keywords mentioned above. After the careful screening of these articles by the two reviewers, 12 individual studies were selected to assess the therapeutic potential of PRE using a meta-analysis.

The main characteristics of the 12 included studies are summarized in Table 1. Four studies reported on the antihypertensive activity of PREs in rats with L-NAME-induced hypertension [14,24,28,29]. Eight studies investigated the antioxidant properties of PREs using DPPH-, ABTS-, and FRAP-scavenging activity [9,11,13,14,16,24–26]. The anticancer activity of PREs was reported in five studies through reductions in cancer cell viability [13,25–27], whereas biocompatibility in normal cell lines was reported in two studies [9,25].

All the studies were conducted in Vietnam (n = 5), Thailand (n = 2), China (n = 1), and Nigeria (n = 4). Most investigations focused on the therapeutic potential of the leaf and stem extracts of *P. roxburghiana*. These plant materials were subjected to various extraction methods, including ethanol, hot water, and cold water, before being tested in vitro and in vivo.

The studies included three major experimental models: L-NAME-induced hypertensive rats, normal cell lines (WS-1 and Vero cells), and cancer cell lines (Caco-2, HepG2, Hep-2, A549, Hep3B, and RAW264.7 cells). Most studies have reported high amounts of bioactive compounds (such as phenolics, flavonoids, anthocyanins, terpenoids, coumarins, and tannins), suggesting favorable antioxidant capacity and biocompatibility.

The extracted data included cell viability (%), DPPH and ABTS scavenging, FRAP activities (IC_{50} values), and antihypertensive parameters, including SBP, DBP, MAP, nitric oxide (NO) levels, catalase activity, and glutathione levels. Pooled analyses were performed to enhance the statistical power and robustness of the evaluated outcomes.

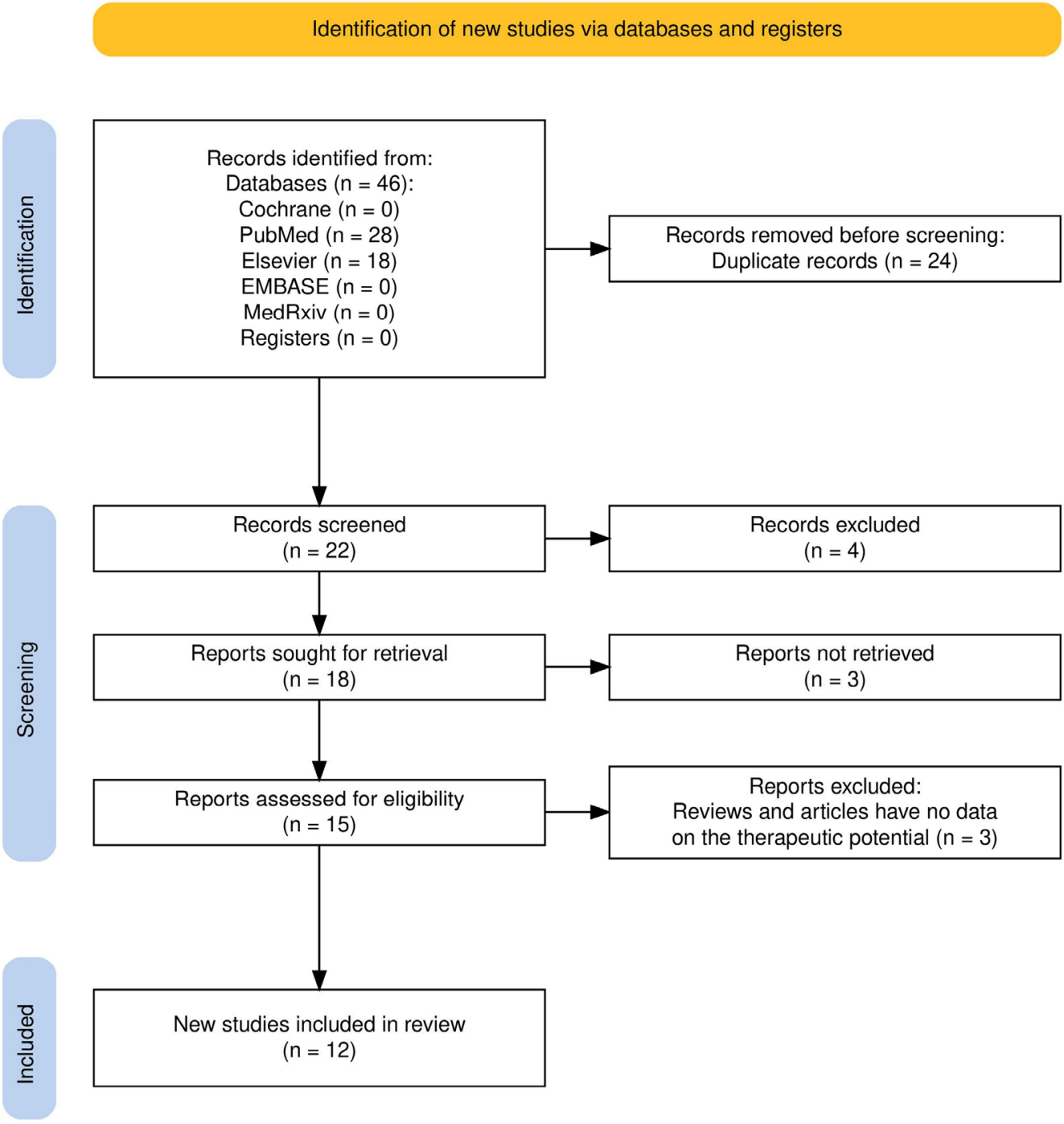


Figure 2. Systematic screening stages of the literature review on *P. roxburghiana* extracts (PREs).

Table 1. Characteristics of the included studies.

Reference	Region	Raw *P. roxburghiana*	Extraction Methods	Physicochemical Properties		Therapeutic Activity	Experimental Subjects	Main Outcomes
				Compounds	Mean ± SD			
Aluko et al. 2025 [29]	Nigeria	Leaves	Water extraction	–	–	Antihypertensive	L-NAME-induced hypertensive rats	SBP, DBP, MAP Serum nitric oxide (NO) levels Malondialdehyde (MDA) Catalase level Glutathione levels
Chen et al. 2025 [13]	China	Leaves	Hot water extraction	–	–	Antioxidant Anticancer	RAW264.7 cell line	Cell viability (%) DPPH scavenging (IC_{50}, μg/mL) ABTS scavenging (IC_{50}, μg/mL) FRAP (IC_{50}, μmol Fe^{2+}/g extract)
Le et al. 2025 [27]	Vietnam	Leaves	Ethanol extraction	–	–	Anticancer	HepG2 cell line	Cell viability (%)
Wichayapreechar et al. 2025 [9]	Thailand	Leaves	Ethanol extraction	Phenolic Flavonoids Anthocyanins, coumarins, and terpenoids	146.72 ± 4.74 (mg/GAE/g) 510.74 ± 7.41 (mgQE/g)	Antioxidant	WS-1 cell line	Cell viability (%) DPPH scavenging (IC_{50}, μg/mL) ABTS scavenging (IC_{50}, μg/mL) FRAP (IC_{50}, μmol Fe^{2+}/g extract)
Aluko et al. 2024a [24]	Nigeria	Leaves	Cold extraction techniques	Tannins, resins, flavonoids, terpenoids, phenols	–	Antihypertensive Antioxidant	L-NAME-induced hypertensive rats	SBP, DBP, MAP Serum NO level DPPH scavenging (IC_{50}, μg/mL) Total antioxidant capacity (TAC, IC_{50}, μg/mL)

Table 1. *Cont.*

Reference	Region	Raw *P. roxburghiana*	Extraction Methods	Physicochemical Properties		Therapeutic Activity	Experimental Subjects	Main Outcomes
				Compounds	Mean ± SD			
Aluko et al. 2024b [28]	Nigeria	Leaves	Aqueous extraction	Tannins, alkaloids, glycosides, flavonoids, sterols	–	Antihypertensive	L-NAME-induced hypertensive rats	Malondialdehyde (MDA) Catalase level Glutathione level
Hang et al. 2024 [11]	Vietnam	Leaves	Hot water extraction	–	–	Antioxidant	–	DPPH scavenging (IC_{50}, μg/mL)
Mai et al. 2020 [26]	Vietnam	Stem and leaves	Hot and cold-water extraction	–	–	Antioxidant Anticancer	A549, Hep3B, and RAW264.7 cell lines	Cell viability (%) DPPH scavenging (IC_{50}, μg/mL)
Aluko et al. 2019 [14]	Nigeria	Leaves	Ethanol extraction	Tannins, resins, phlobatannins, flavonoids, sterols, phenolics, alkaloids, terpenoid	–	Antihypertensive Antioxidant	L-NAME-induced hypertensive rats	SBP, DBP, MAP Serum NO level MDA level Catalase level Glutathione level DPPH scavenging (IC_{50}, μg/mL) Total antioxidant capacity (TAC, IC_{50}, μg/mL)
Quan et al. 2016 [16]	Vietnam	Leaves and stems	Ethanol extraction	Chlorophyll Carotenoid Anthocyanin Phenolics Flavonoids	0.63 ± 0.023 (mg/g) 0.025 ± 0.001(mg/g) 0.244 ± 0.003 (mg C3GE/g) 21.83 ± 0.74 (mg GAE/g) 5.82 ± 0.50 (mg RE/g)	Antioxidant	–	DPPH scavenging (IC_{50}, μg/mL)

Table 1. *Cont.*

Reference	Region	Raw *P. roxburghiana*	Extraction Methods	Physicochemical Properties		Therapeutic Activity	Experimental Subjects	Main Outcomes
				Compounds	Mean ± SD			
Phaopongthai et al. 2015 [25]	Thailand	Leaves	Ethanol extraction	–	–	Biocompatibility Antioxidant	Vero, Caco-2, HepG2, and Hep-2 cell line	Cell viability (%) DPPH scavenging (IC_{50}, μg/mL)
Thuy et al. 2013 [15]	Vietnam	Leaves	Ethanol extraction	–	–	Anticancer	HepG2 cell line	Cell viability (%)

3.2. Quality Assessment of Included Studies

Given the inclusion of both in vitro and in vivo preclinical studies, no universally validated risk-of-bias tool was fully applicable. Therefore, an adapted checklist was developed based on established methodological principles commonly used in preclinical systematic reviews to assess reporting transparency, experimental design, and outcome reliability.

The quality scores of the included studies ranged from 6 to 9 (Table 2). Most studies were classified as moderate to high quality, with common methodological limitations, including the inadequate reporting of replication and the absence of positive controls in some assays.

Table 2. Quality assessment of included studies.

Reference	Quality Assessment Domains									Quality Score
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	
Aluko et al. 2025 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Chen et al. 2025 [13]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	7
Le et al. 2025 [27]	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Wichayapreechar et al. 2025 [9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Aluko et al. 2024a [24]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8
Aluko et al. 2024b [28]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	8
Hang et al. 2024 [11]	Yes	Yes	No	Yes	No	Yes	No	No	Yes	6
Mai et al. 2020 [26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Aluko et al. 2019 [14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Quan et al. 2016 [16]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	6
Phaopongthai et al. 2015 [25]	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	6
Thuy et al. 2013 [15]	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	6

Q1. Test system; Q2. Sample preparation; Q3. Controls; Q4. Replication; Q5. Concentration; Q6. Concentration; Q7. Statistics; Q8. Data clarity; Q9. Transparency.

3.3. In Vitro Antioxidant Activities

3.3.1. DPPH Free Radical-Scavenging Activity

Eight studies reported DPPH radical-scavenging activity expressed as IC_{50} (μg/mL) [9,11,13,14,16,24–26]. The random-effects meta-analysis yielded a pooled geometric mean IC_{50} of 3.57 [0.96; 13.34] μg/mL (Table 3). Based on commonly used classification criteria for DPPH assays (IC_{50} < 50 μg/mL), these findings indicate that PRE demonstrates measurable strong antioxidant activity. However, substantial heterogeneity (I^2 = 99.59%) indicated considerable variability across the studies.

A leave-one-out (LOO) sensitivity analysis was conducted to evaluate the influence of individual studies on the pooled DPPH IC_{50} estimates (Figure 3A and Table S2). Sequential omission of each study resulted in pooled IC_{50} values ranging from 2.57 to 5.02 μg/mL, indicating that no single study disproportionately influenced the overall effect size. However, heterogeneity remained consistently high (I^2 = 99%) across all LOO models. These findings suggest that variability is unlikely to be driven by a single influential study but rather reflects broader methodological or biological differences among experiments.

Table 3. Summary of the pooled standardized mean differences (SMDs) and pooled IC_{50} of the PRE treatment and control groups.

Therapeutic Activities	Comparisons		Pooled SMDs/IC_{50} (95%)	I^2 (%)
Antioxidant	DPPH scavenging		3.57 [0.96; 13.34]	99.59
	ABTS scavenging		91.96 [47.30; 178.78]	83.8
	FRAP scavenging		63.39 [0.29; 13,992]	99.82
Biocompatibility	Cell viability		0.77 [−0.38; 1.92]	0
Anticancer	Cell viability		2.28 [0.54, 4.03]	63
Antihypertensive	Blood pressure parameters	SBP	12.76 [6.35; 19.18]	0
		DBP	7.74 [3.55; 11.94]	0
		MAP	11.21 [5.40; 17.02]	4
		Subgroup analysis	9.70 [6.73; 12.67]	0
	Oxidative stress biomarkers	MDA level	4.56 [2.25; 6.86]	3
		Serum NO level	−1.17 [−2.22; −0.12]	0
		SOD level	−4.11 [−12.77; 4.54]	88
		Catalase level	−1.19 [−2.22; −0.16]	0
		Glutathione level	−2.76 [−4.51; −1.00]	19
		Subgroup analysis	−0.79 [−2.08; 0.50]	73

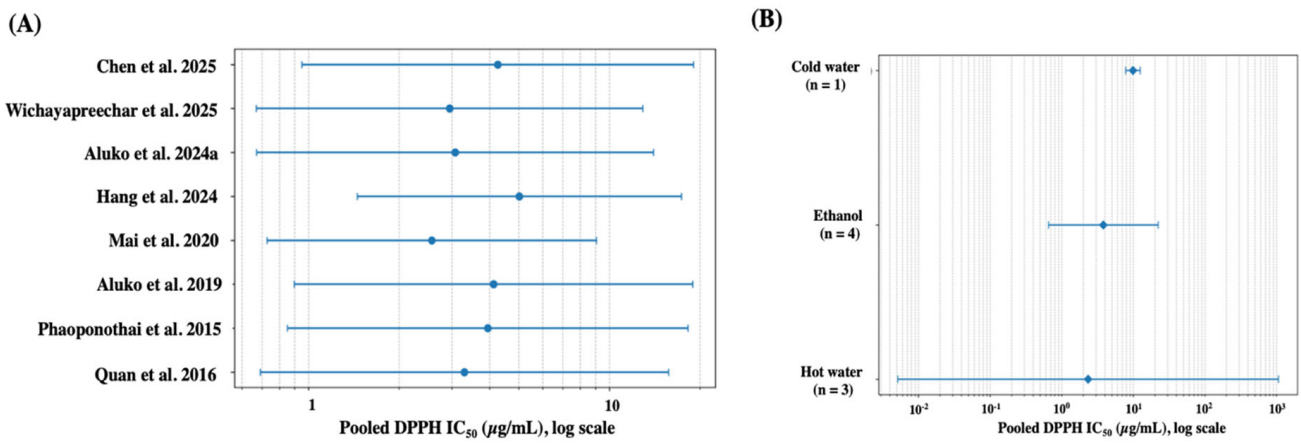


Figure 3. (**A**) Leave-one-out sensitivity analysis of DPPH-scavenging activity expressed as IC_{50} (μg/mL) [9,11,13,14,16,24–26]. (**B**) Subgroup-forest plot of DPPH-scavenging activity (IC_{50}, μg/mL) stratified by the extraction method.

Additionally, subgroup analysis using the extraction method showed differences in the pooled DPPH IC_{50} values (Figure 3B and Table S3). Ethanol extracts (n = 4) showed a pooled IC_{50} of 3.82 [0.65; 22.25] μg/mL, with moderately reduced heterogeneity compared with the overall analysis. Hot water extracts (n = 3) yielded a pooled IC_{50} of 2.34 μg/mL; however, the wide CI indicates imprecision in the estimate, and heterogeneity remained high. Only one study employed cold-water extraction, precluding a heterogeneity assessment.

The results show that the extraction method may contribute to variability in reported DPPH-scavenging activity, with ethanol extraction accounting for some of the observed differences between studies. Nevertheless, the consistently high heterogeneity suggests that additional factors, such as plant materials, extraction conditions, solvent concentrations, and assay protocols, likely contribute to the observed variability.

Importantly, these results are derived from preclinical in vitro assays and should therefore be interpreted within that experimental context.

3.3.2. ABTS Free Radical-Scavenging Activity

The ABTS-scavenging capacity of PRE was evaluated by analyzing the IC_{50} values (μg/mL) from two studies (Figure 4) [9,13]. A random–effects meta-analysis yielded a pooled IC_{50} of 91.96 [47.30; 178.78] μg/mL. According to the referenced classification criteria for antioxidant assays, this pooled estimate falls within a range generally interpreted as moderate activity. The wide 95% CI suggests imprecision and variability in the effect estimates between studies. This substantial heterogeneity (I^2 = 83.8%) may be attributed to differences in the extraction conditions and ABTS assay protocols that were used.

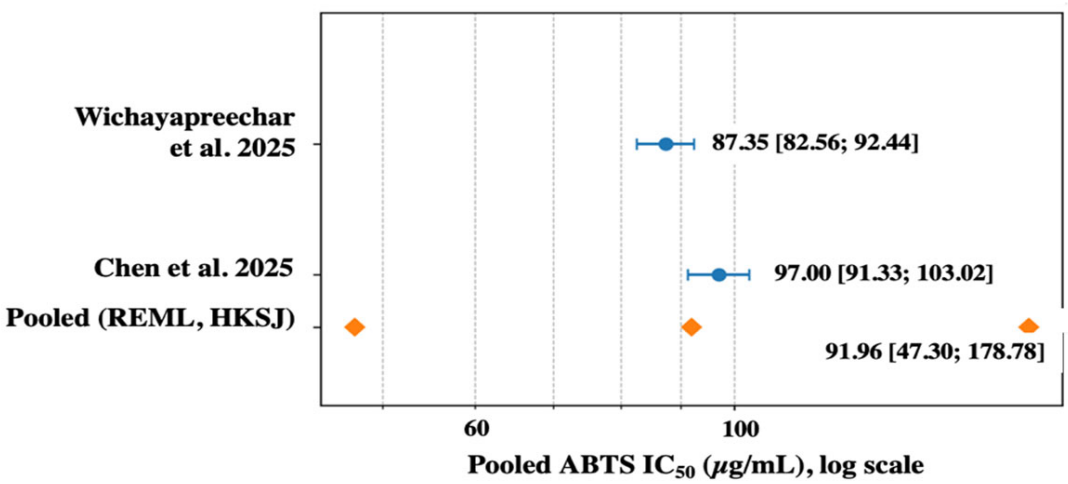


Figure 4. Forest plot of the ABTS radical-scavenging activity expressed as IC_{50} (μg/mL) [9,13].

3.3.3. FRAP Activity

According to the meta-analysis of the two included studies, the pooled FRAP IC_{50} was 63.39 [0.29; 13,992] μmol Fe^{2+}/g extract (Figure 5). The extremely wide CI reflects substantial uncertainty, primarily owing to the limited number of available studies; therefore, the pooled estimates should be interpreted with caution.

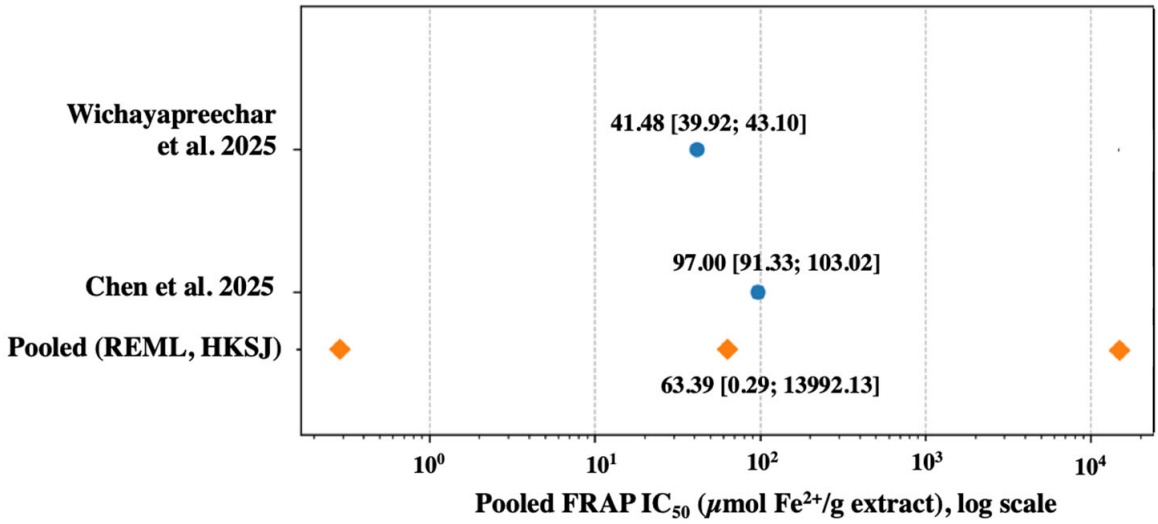


Figure 5. Forest plot of FRAP expressed as μmol Fe^{2+}/g extract [9,13].

3.4. Biocompatibility

Only two studies reported the biocompatibility of PREs in normal cell lines (WS-1 and Vero cells) [9,25]. The biocompatibility of PRE was analyzed by comparing the PRE-treated and control groups in the two cell models (Figure 6 and Table 3). The meta-analysis yielded a pooled SMD of 0.77 [−0.38; 1.92], with no observed heterogeneity (I^2 = 0%). When the CI value was zero, no statistically significant difference in cell viability was observed between the PRE-treated and control groups. These results suggest that PREs did not demonstrate a statistically detectable reduction in viability in the tested normal cell lines. However, the analysis is based on only two in vitro studies, and the relatively wide CI reflects uncertainty in the pooled estimate. Therefore, conclusions regarding biocompatibility should be interpreted cautiously.

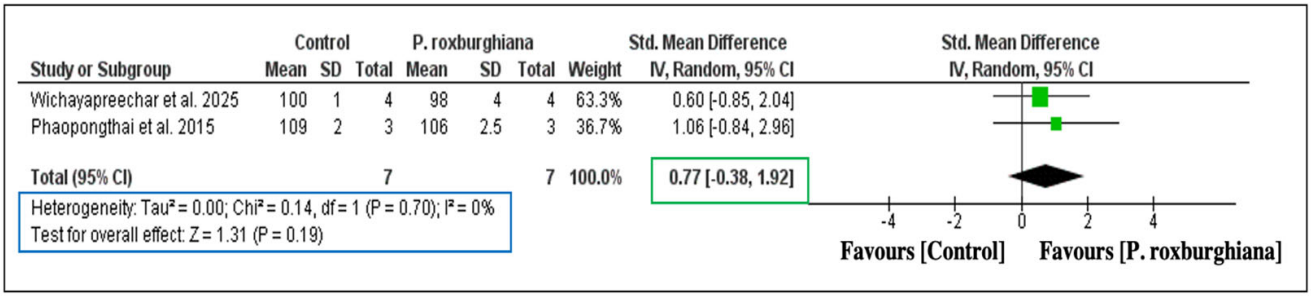


Figure 6. Comparison of the viability (%) of normal cells between the control and the PRE–treatment groups [7,19].

3.5. Anticancer Activity

The cytotoxicity of PREs on cancer cells was evaluated by comparing cell viability (%) between the PRE and control groups using a random-effect model (Figure 7A and Table 3) [13,15,25–27]. The results indicated a significant difference in cell viability between the two groups (SMD = 2.28 [0.54, 4.03]), demonstrating that the PREs resulted in a statistically significant reduction in cell viability in PRE-treated groups compared with controls. However, this result was not statistically significant owing to considerable heterogeneity (I^2 = 63%). This may reflect differences in cancer cell lines, extract compositions, concentrations, and exposure durations across studies.

Meta-regression was conducted using study-level moderators, including dose, extraction type, and cell line category (Figure 7B and Table S4), to explore the sources of this heterogeneity. The findings showed that the cell line category contributed to the primary heterogeneity (omnibus p = 0.004). A near-complete attenuation of the residual variance was observed between the effects after accounting for the cell line groups. Specifically, effect sizes varied significantly across cell lines, with A549 lung cancer cells showing markedly larger SMDs than liver (Hep*), immune (RAW 264.7), or colon (Caco-2) cells. Including the cell line group as a moderator resulted in an almost complete reduction in the between-study variance. By contrast, neither the dose (p = 0.370) nor the extraction type (p = 0.707) significantly explained the heterogeneity.

These findings suggest that the magnitude of the observed cytotoxic effects varies according to cancer cell type under in vitro conditions, rather than by variations in the dose or extraction method. Nevertheless, interpretation should remain cautious, as multiple effect sizes were derived from individual studies, which may introduce within-study correlation. In addition, the evidence is limited to preclinical cell-based assays and does not establish clinical relevance.

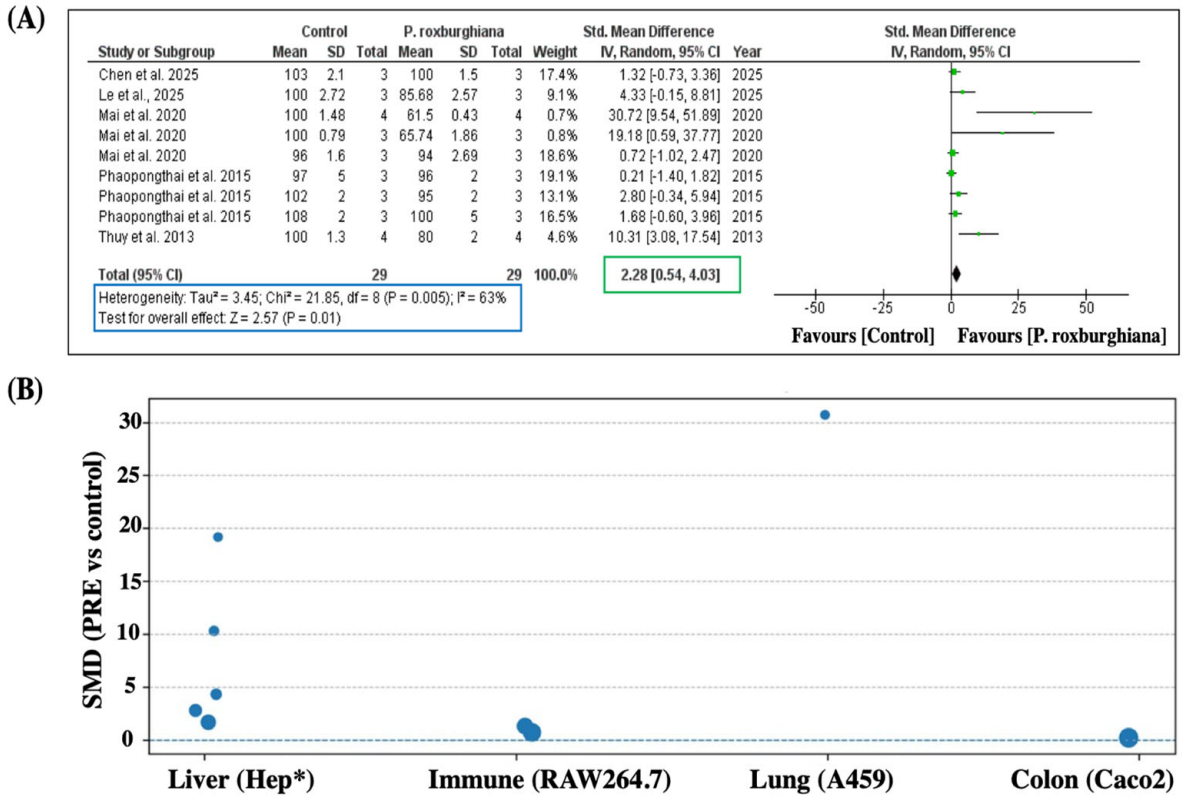


Figure 7. (**A**) Comparison of the cell viability (%) of cancer cells between the control and PRE-treated groups [11,13,19–21]. (**B**) Bubble plot of the meta-regression examining the influence of cell line category on cancer cell viability outcomes following PRE treatment.

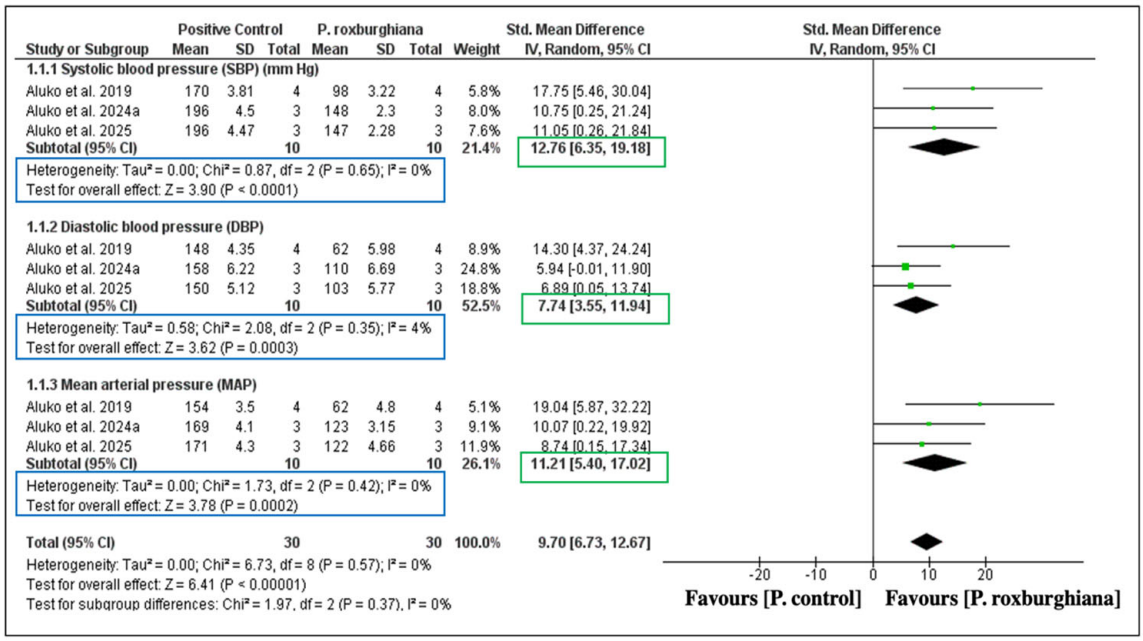
3.6. Antihypertensive Activity

The antihypertensive activity of PRE was reported in four studies [14,24,28,29]. In these studies, L-NAME-induced hypertensive rats were used as validated experimental models of hypertension. Hypertensive parameters were systematically assessed in both positive control and PRE–treatment groups. The primary outcomes were categorized into hemodynamic (SBP, DBP, and MAP) and oxidative stress-related (MDA, NO, SOD, catalase, and glutathione) biomarkers, based on biological and methodological differences. Separate subgroup analyses were conducted for these outcome categories to account for biological and methodological differences.

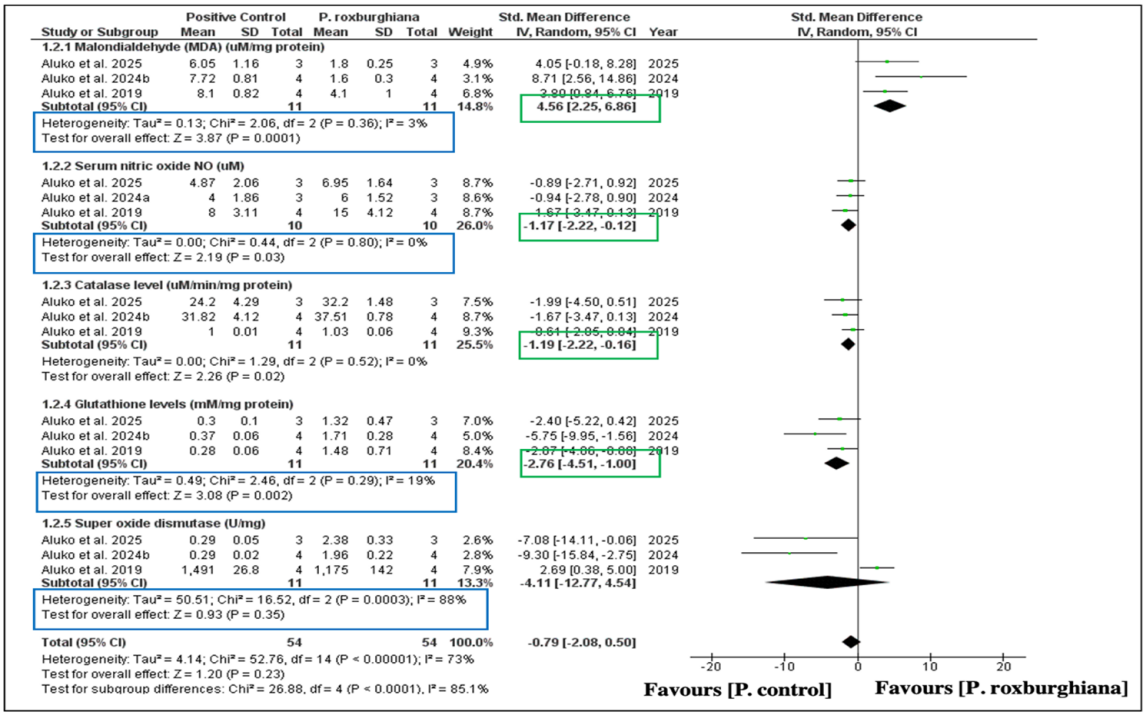
In the blood–pressure parameter subgroup analysis, the pooled effect estimates showed lower blood pressure values in PRE-treated rats compared with the positive control (overall SMD = 9.70 [6.73; 12.67]), with no detected heterogeneity ($I^2 = 0$). Specifically, the results indicated a significant reduction in SBP, DBP, and MAP in the PRE group compared to the positive control group without heterogeneity ($I^2 = 0$–4%) (Figure 8A and Table 3). This finding suggests that the antihypertensive effect of PRE is stable and reproducible across studies, supporting its potential to mitigate hypertension associated with NO deficiency.

Additionally, a subgroup meta-analysis was conducted to evaluate the effects of PRE on five oxidative stress-related biomarkers (Figure 8B and Table 3). As shown in Table 3, MDA levels significantly decreased following PRE administration, with minimal heterogeneity ($I^2 = 3\%$), indicating a reduction in lipid peroxidation. By contrast, serum NO levels were significantly increased in the PRE group compared with the positive control (SMD = −1.17 [−2.22; −0.12]), with no detectable heterogeneity ($I^2 = 0\%$), suggesting a partial restoration of NO bioavailability under L-NAME-induced conditions. Similarly, catalase activity and glutathione levels were significantly enhanced in the PRE group,

with low heterogeneity (I^2 = 0–19%). However, SOD activity did not differ significantly between groups (SMD = −4.11 [−12.77; 4.54]) and exhibited substantial heterogeneity (I^2 = 88%), indicating considerable interstudy variability. When all biomarkers were combined, the overall pooled effect was not statistically significant, and heterogeneity across biomarker subgroups was substantial (I^2 = 73%). Overall, these results indicate that PRE administration in L–NAME-induced hypertensive rats is associated with changes in selected oxidative stress markers and blood pressure parameters.



(**A**)



(**B**)

Figure 8. Subgroup analysis evaluating the efficacy of PRE in reducing hypertensive symptoms in L-NAME-induced hypertensive rats. (**A**) Blood pressure parameters. (**B**) Oxidative stress-related biomarkers [14,24,28,29].

4. Analysis Bias

Funnel plots were constructed to detect publication biases (Figure 9). Visual inspection of the funnel plots revealed varying degrees of asymmetry across outcomes. Minimal asymmetry was observed in cell viability, suggesting a low risk of publication bias. By contrast, cancer cell viability and blood pressure outcomes exhibited notable asymmetry, indicating the potential for small-study effects and publication bias. For oxidative stress biomarkers, funnel plot asymmetry appeared to be largely attributable to biomarker-specific and methodological heterogeneity, rather than selective reporting. Overall, although the direction of the effects was consistent, the magnitude of the pooled estimates, particularly for anticancer and antihypertensive outcomes, should be interpreted with caution. In addition, the results indicated that the number of studies included in each analysis criterion was small, leading to underestimated meta-analysis results and publication biases. In the future, a meta-analysis of numerous prospective studies should be conducted to increase statistical significance and reduce publication bias.

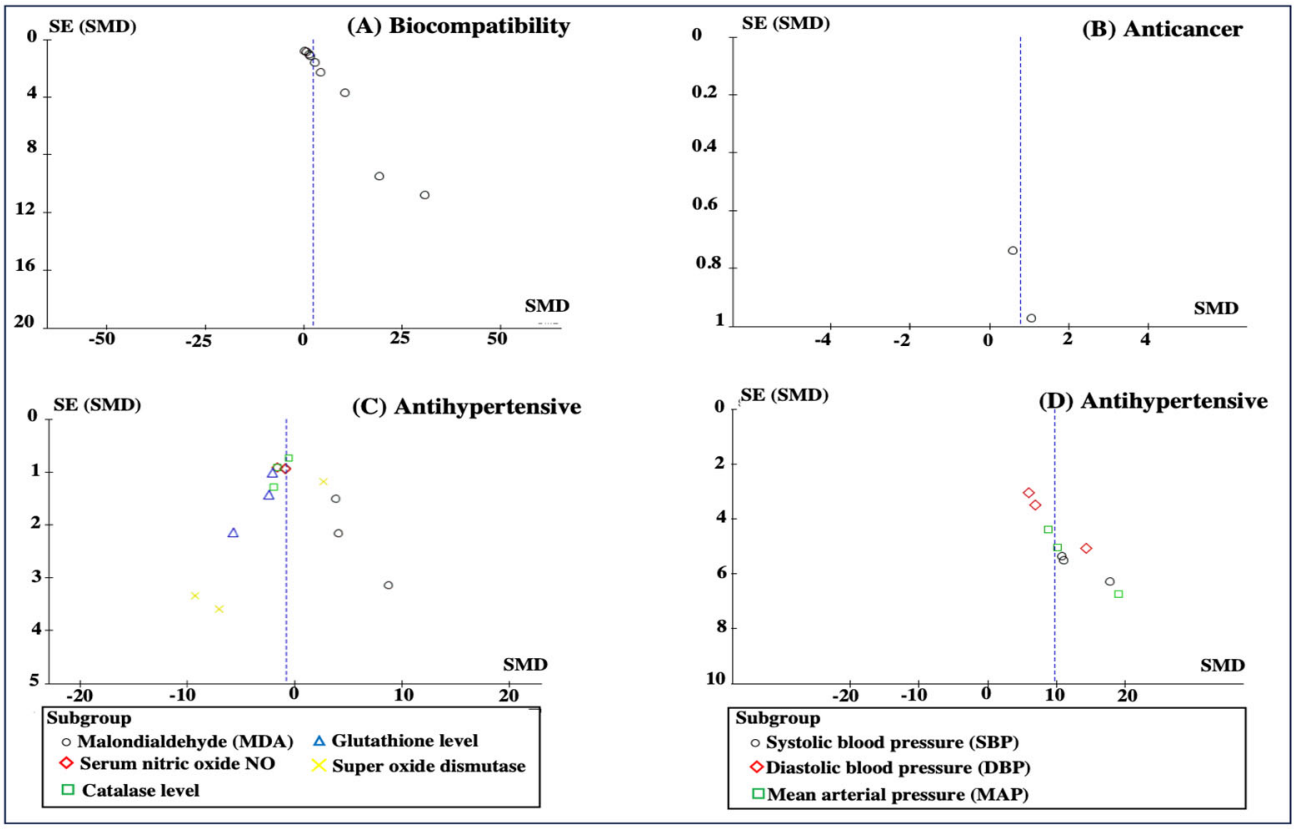


Figure 9. Publication biases of the included studies on the effectiveness of PRE in therapeutic applications.

5. Discussion

This systematic review and meta-analysis provides a comprehensive quantitative synthesis of the therapeutic potential of PRE considering 12 in vitro and in vivo studies. This study covers multiple biological domains, including antioxidants, biocompatibility, anticancer, and antihypertensive properties. By integrating data from multiple experimental systems, this review provides a structure overview of the current preclinical evidence base; however, the findings remain limited to laboratory settings.

The pooled IC_{50} values for DPPH, ABTS, and FRAP assays suggest that PRE exhibits measurable in vitro antioxidant activity. Specifically, the low pooled DPPH and

ABTS IC_{50} values (~ 3.57 and 91.96 μg/mL, respectively) indicate the capacity of PRE constituents to participate in hydrogen atom transfer (HAT) and single-electron transfer (SET) mechanisms [42,43]. In addition, the pooled IC_{50} value for FRAP was 63.39 μg/mL, confirming that the ability to reduce ferric (Fe^{3+}) ions to ferrous (Fe^{2+}) ions reflects electron-donating properties, which may contribute to redox modulation under experimental conditions [42,43]. This reducing capacity highlights the role of PRE constituents as electron donors, capable of stabilizing oxidized intermediates and interrupting oxidative chain reactions [42,43]. In biological systems, excessive redox-active metal ions can catalyze the formation of reactive oxygen species (ROS) via Fenton and Haber–Weiss reactions [44]. By modulating redox states, PRE may indirectly reduce ROS generation, thereby contributing to secondary antioxidant defenses beyond its direct radical-scavenging activity.

The high antioxidant activity of PRE is largely attributed to its high phytochemical content, particularly phenolics, flavonoids, and anthocyanins [4,42,45]. These bioactive compounds operate via both the HAT- and SET-based pathways, enabling broad-spectrum radical scavenging under different oxidative conditions [42,43,46]. Anthocyanins, phenolics, and flavonoids possess conjugated aromatic systems and hydroxyl groups that stabilize radicals [45,46], while polysaccharides indirectly exert antioxidant effects by modulating cellular redox homeostasis [47]. These phytochemicals may upregulate endogenous antioxidant systems (e.g., glutathione, SOD, and catalase), thereby enhancing cellular resilience without inducing oxidative imbalance [47,48].

Despite the low pooled IC_{50} values, the meta-analyses of antioxidant activities did not reach statistical significance owing to considerable between-study heterogeneity (I^2 ~ 83–99%). In terms of DPPH-scavenging activity, extremely high heterogeneity persisted even after conducting an LOO sensitivity analysis, indicating that the variability among studies was systematic rather than driven by any single influential study. This large heterogeneity is likely attributable to methodological differences among studies, including extraction methods, assay conditions (e.g., DPPH concentration and incubation time), solvent polarity, and the geographic origin of raw materials. Moreover, subgroup analysis identified the extraction method as a key factor affecting DPPH-scavenging activity. Ethanol extraction yielded more homogeneous antioxidant activity, whereas hot water extraction showed greater variability. By contrast, the ABTS and FRAP analyses were performed in only two studies, leading to statistically unstable heterogeneity estimates and very wide CIs. Although the pooled estimates provide preliminary insight into antioxidant capacity, the small number of included studies substantially limits the statistical power and precision, necessitating cautious interpretation.

The biocompatibility of PRE was confirmed by comparing the survival rates of normal cells (WS-1 and Vero) in control and PRE-treated groups. The pooled analysis did not demonstrate a statistically significant difference in cell viability, with no detectable heterogeneity (SMD = 0.77 [−0.38; 1.92], I^2 = 0). These findings suggest that PRE did not produce measurable cytotoxic effects in the tested normal cell models. Experimental evidence indicates that PRE possesses antioxidant properties that may contribute to redox modulation in cellular systems [4]. This selective redox modulation protects normal cells from oxidative damage without surpassing the pro-oxidant threshold necessary to trigger apoptosis or necrosis in healthy tissues [19,42,45]. In addition, PRE did not markedly disrupt mitochondrial membrane potential or impair ATP production in normal cells [4,49]. By maintaining mitochondrial stability, PRE supports normal cellular metabolism and prevents the activation of intrinsic apoptotic pathways in nontransformed cells, thereby avoiding genotoxic damage. These observations may reflect preservation of mitochondrial function under in vitro conditions [4,49]. Although the current in vitro findings indicate

high biocompatibility in normal cells, further in vivo and long-term safety studies are required to confirm these effects under physiological conditions.

Although PRE exhibits antioxidant activity, it can paradoxically act as a pro-oxidant in cancer cells. Cancer cells often maintain elevated basal ROS levels because of their high metabolic and proliferative demands [50,51]. Under such conditions, exposure to *P. roxburghiana*-derived compounds may further increase intracellular ROS, potentially exceeding cellular tolerance thresholds and contributing to oxidative stress-associated cell death [27,50,51]. In addition, excess ROS and phytochemical–mitochondrial interactions between cancer cells and PRE can disrupt the mitochondrial membrane potential, leading to cytochrome C release, caspase-9 and caspase-3 activation, and apoptotic DNA fragmentation [52]. These intrinsic mechanisms are commonly observed in anticancer agents and are particularly evident in lung and liver cancer cell lines [9,13]. Additionally, PRE bioactive compounds may suppress the inflammatory and pro-survival pathways (e.g., NF-κB and MAPK), thereby downregulating anti-apoptotic proteins, enhancing sensitivity to oxidative and metabolic stress, and diminishing proliferative capacity [53,54]. These proposed mechanisms provide a biological framework for interpreting the pooled findings, which showed a statistically significant reduction in cancer cell viability in PRE-treated groups compared with controls (SMD = 2.28 [0.54, 4.03], I^2 = 63%). However, given the moderate heterogeneity and reliance on in vitro models, these results should be interpreted cautiously. Meta-regression analysis suggested that variability in effect size was primarily associated with differences among cancer cell lines, rather than dosage or extraction method within the available dataset.

This study also provides quantitative evidence supporting the antihypertensive potential of PRE, as demonstrated by the consistent reductions in blood pressure parameters and favorable modulation of oxidative stress-related biomarkers. In L-NAME-induced hypertensive rats, the inhibition of NO synthesis resulted in reduced NO bioavailability, increased vascular resistance, sustained vasoconstriction, and elevated blood pressure [29,55,56]. The meta-analysis found that PRE treatment remarkably ameliorated these pathological changes, with highly significant and homogeneous effects across the core hemodynamic parameters (I^2 = 0–4%). In addition to its direct hemodynamic effects, the antihypertensive activity of PRE appears to be closely linked to its antioxidant and redox-modulating properties [29]. It was found that PRE significantly reduces MDA levels and enhances catalase, NO, and glutathione levels, reflecting the attenuation of lipid peroxidation and enhancement of endogenous antioxidant defenses [14,24,28]. Given the central role of oxidative stress in endothelial dysfunction and hypertension, restoring redox balance and NO bioavailability is likely a key mechanism underlying the antihypertensive effects of PRE [57,58].

The methodological quality of the included studies may influence the magnitude and reliability of the pooled estimates. Variability in experimental design, limited reporting of randomization or blinding procedures, small sample sizes, and heterogeneity in extraction protocols could introduce bias or inflate effect sizes. Although a structured quality assessment was conducted, the adapted nature of the checklist and the limited number of eligible studies restrict the ability to perform formal quality-based stratified analyses. Consequently, the pooled results should be interpreted as indicative of overall biological trends rather than definitive quantitative conclusions.

In summary, this systematic review synthesizes current preclinical evidence indicating that PRE demonstrates antioxidant activity, modulation of oxidative stress-related biomarkers, and reductions in experimental cancer cell viability and blood pressure parameters (Figure 10). These findings are derived from in vitro and animal models and should be interpreted within those experimental contexts. Given the established role of

oxidative stress in endothelial dysfunction, hypertension, and carcinogenesis, the observed redox-modulating properties of PRE may warrant further investigation in more advanced experimental systems. The available data suggest that PRE influences oxidative and inflammatory pathways under laboratory conditions; however, the translational relevance of these findings remains to be determined. Future studies incorporating standardized extraction methods, pharmacokinetic evaluation, safety assessment, and well-designed animal models will be essential to clarify the potential biological significance of PRE beyond preclinical observations.

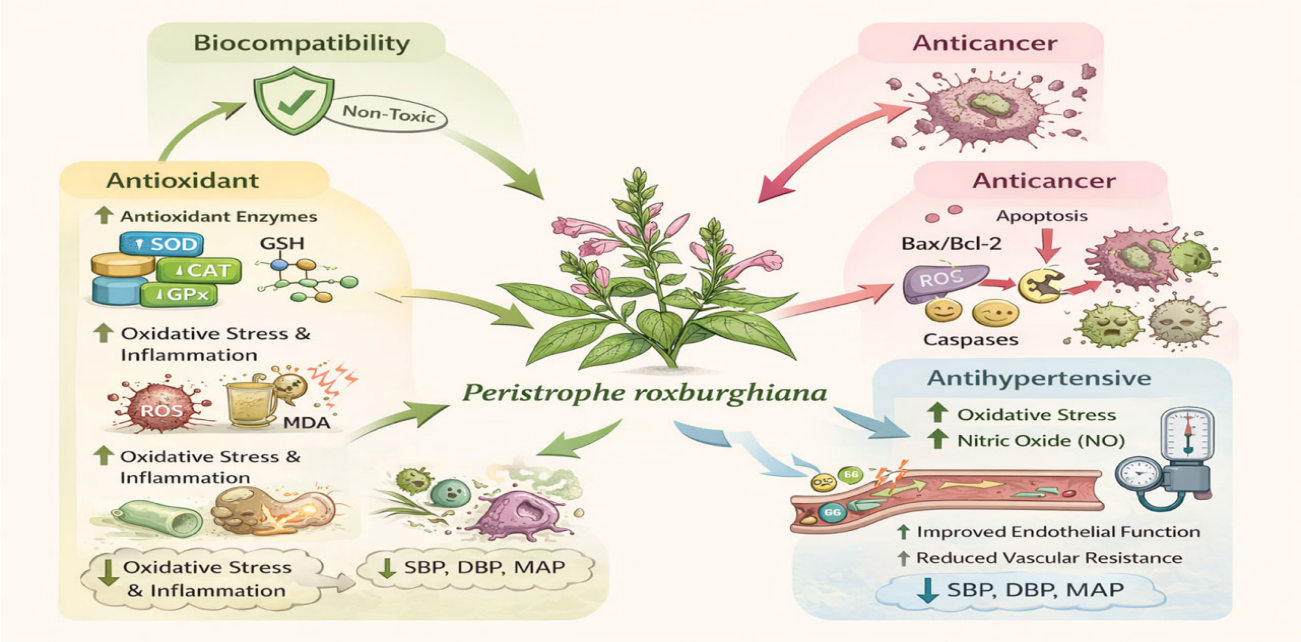


Figure 10. Schematic of the biocompatibility and antioxidant, anticancer, and antihypertensive properties of PRE.

6. Limitations of Study

This meta-analysis had several limitations that should be considered when interpreting the findings. First, the number of included studies was relatively small (12 studies), leading to small-sample-size effects and the low reliability of the analytical results. Second, the evidence base consisted solely of in vitro and in vivo studies, precluding the direct extrapolation of the promising benefits of PRE in clinical settings. Third, several included studies were not originally designed to evaluate therapeutic effects, but rather focused on industrial or food-related applications. Consequently, the therapeutic implications derived from these studies are based on secondary biological endpoints, and the findings should be interpreted cautiously in the context of preclinical evidence. Fourth, although sensitivity and subgroup analyses were performed, substantial heterogeneity persisted for some outcomes, potentially reducing the precision of the pooled estimates. Specifically, variability in extraction methods, dosing regimens, and outcome measurements may contribute to this heterogeneity. Finally, potential publication bias could not be reliably assessed owing to the limited number of eligible studies, underscoring the need for more standardized and well-powered preclinical investigations to confirm the therapeutic potential of PRE.

7. Conclusions

This systematic review and meta-analysis provides a comprehensive synthesis of the preclinical evidence regarding the biological activities of PREs, owing to their potent antioxidant activity and high biocompatibility. The pooled analysis revealed strong an-

tioxidant capacity, as evidenced by the low pooled IC_{50} values in DPPH, ABTS, and FRAP assays. Importantly, PRE exhibited a safety profile, with no cytotoxicity in normal cell lines and consistent biocompatibility across studies. By contrast, PREs were associated with reduced cancer cell viability in vitro, potentially through oxidative stress-mediated and apoptosis-related mechanisms. Additionally, in vivo studies using hypertensive animal models suggest that PREs may contribute to improvements in blood pressure parameters and oxidative stress-related biomarkers. Despite these promising findings, the substantial heterogeneity, predominance of in vitro and in vivo study designs, and limited number of available studies necessitate cautious interpretations. Consequently, the present results do not support direct clinical inference, but rather highlight the potential biological relevance of PREs as candidates for further preclinical and mechanistic investigation. Future research should prioritize the development of standardized extraction protocols, clearly defined dosing frameworks, and harmonized antioxidant and bioactivity assay methodologies. Consistent reporting standards, including detailed phytochemical characterization and concentration normalization, will substantially enhance inter-study comparability. As the evidence base expands, larger and methodologically rigorous datasets will enable more subgroup analyses and meta-regression approaches, thereby enhancing the precision of pooled estimates and strengthening the translational relevance of preclinical findings.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app16042041/s1, Table S1. Databases search strategies. Table S2. A leave-one-out (LOO) sensitivity analysis of DPPH radical-scavenging activity (IC_{50} μg/mL). Table S3. Subgroup analysis of DPPH radical-scavenging activity (IC_{50} μg/mL). Table S4. Characteristics of meta-regression studies on cancer cell survival under the influence of PREs. Table S5. PRISMA 2020 main checklist. Table S6. PRIMSA Abstract Checklist.

Author Contributions: L.T.N.N. and Y.-C.L. planned the study and contributed the main ideas. L.T.N.N. was principally responsible for collecting data and writing of the manuscript. Y.-C.L. commented on and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ABTS	2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)
ATP	Adenosine triphosphate
CI	Confidence interval
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
FRAP	Ferric Reducing Antioxidant Power
HAT	Hydrogen atom transfer
IC_{50}	Half-maximal inhibitory concentration
L-NAME	N_{ω}-nitro-L-arginine methyl ester hydrochloride

MAD	Malondialdehyde
MAP	Mean arterial pressure
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
PREs	*Peristrophe roxburghiana* extracts
REML	Restricted maximum likelihood
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SET	Single-electron transfer
SMDs	Standardized mean differences
SOD	Super oxide dismutase

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