International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 107-118 www.ijdmsrjournal.com ISSN: 2582-6018

The Role of Proanthocyanidins in Enhancing Resin–Dentin Bonding: A Systematic Review and Meta-Analysis

Hassan Ihab Hasanein*, Ahmed Z.elhoshy**, Heba Salah eldin-Hamza***
Prof. of Conservative Dentistry, faculty of dentistry, Cairo University

Date of Submission: 20-11-2025 Date of Acceptance: 30-11-2025

ABSTRACT
Background: Degradation of the resin–dentin interface remains a major limitation in adhesive dentistry, driven by collagen breakdown, hydrolysis, and endogenous matrix metalloproteinase (MMP) activity. Proanthocyanidins (PAs), natural collagen cross-linkers with antimicrobial and MMP-inhibitory properties, have been proposed as biomodifiers to enhance hybrid layer integrity and long-term bond performance.
Aim: To systematically evaluate and quantitatively synthesize the effect of proanthocyanidin application—whether as a primer, etchant additive, or adhesive component—on resin–dentin bond strength and interfacial durability.
Methods: A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar was performed for studies evaluating PA-treated dentin compared with untreated controls. Eligibility included in-vitro, in-situ, and clinical studies reporting immediate or aged bond strength, nanoleakage, interfacial nanomechanics, or MMP activity. Data were extracted for standardized mean differences (SMD), and a random-effects meta-analysis was conducted. The risk of bias was assessed using RoBDEMAT and modified CONSORT criteria where applicable.
Results: Out of the retrieved studies, those meeting inclusion criteria consistently demonstrated that PA application significantly improved immediate resin–dentin bond strength compared with controls (moderate positive pooled effect). PA primers—especially at ~10% concentration with 30–60 s application—produced the most stable hybrid layers and reduced nanoleakage after aging. Aging periods ranging from 6 to 30 months showed a smaller reduction in bond strength in PA groups versus controls, supported by enhanced interfacial modulus and substantial suppression of MMP activity. Limited clinical evidence indicated improved interfacial stability but no definitive increase in restoration retention.
Conclusion: Proanthocyanidins provide a beneficial biomodification strategy for enhancing resin–dentin bonding by improving immediate adhesive performance and preserving hybrid layer integrity during aging. While laboratory evidence is strong, standardized clinical protocols and long-term clinical trials are needed to confirm their translational effectiveness in routine restorative dentistry.

Keywords: proanthocyanidins, resin–dentin bonding, biomodification, hybrid layer, collagen cross-linking, meta-analysis, adhesive dentistry.
Core MeSH terms: Proanthocyanidins, Dental Bonding, Dentin-Bonding Agents, Dentin, Composite Resins, Dental Restoration, Permanent

I. INTRODUCTION:

The durability of the resin–dentin interface remains one of the major challenges in adhesive dentistry. Although current adhesive systems achieve high immediate bond strengths, the hybrid layer is highly susceptible to long-term degradation. This deterioration is attributed primarily to hydrolysis of resin components, incomplete resin infiltration into demineralized collagen, and the activation of endogenous matrix metalloproteinases (MMPs) and cysteine cathepsins that progressively break down exposed collagen fibrils (1–4). Such enzymatic and hydrolytic degradation leads to reduced bond strength, increased nanoleakage, and premature failure of resin restorations.

To address these limitations, biomodification of dentin collagen has emerged as a promising strategy. Proanthocyanidins (PAs), naturally occurring polyphenolic flavonoids, exhibit strong collagen-cross-linking capacity, antioxidant activity, and potent inhibition of dentin MMPs (5–8). Their ability to induce exogenous collagen cross-links, stabilize the organic matrix, and reduce water sorption has been shown to enhance the mechanical properties of demineralized dentin (9–11). PA treatment also increases the elastic modulus of the hybrid layer and strengthens the underlying dentin substrate, as demonstrated in nanoindentation and interfacial fracture-toughness experiments (12,13).

Several in-vitro studies have reported significant improvements in immediate and aged resin–dentin bond strength following PA application, particularly when used as a primer

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 107-118 www.ijdmsrjournal.com ISSN: 2582-6018

after phosphoric-acid etching (14–17). Enhanced resistance to long-term degradation has been attributed to PA-mediated suppression of MMP-induced collagen breakdown and reduced nanoleakage under accelerated and natural aging conditions (12,15). Furthermore, PA-containing etchants and adhesives have demonstrated improved hybrid-layer morphology, decreased permeability, and increased interfacial stability (18–20). However, despite promising laboratory evidence, clinical trials remain limited and show inconsistent outcomes, with some studies reporting comparable retention rates between PA-treated and untreated restorations (21).

Given the growing interest in dentin biomodification and the wide variability in PA concentrations, application times, and adhesive strategies, a comprehensive synthesis of the available evidence is needed. This systematic review and meta-analysis aim to evaluate the effect of proanthocyanidin application on the resin–dentin interface by assessing immediate and aged bond strength, hybrid-layer stability, nanomechanical properties, and interfacial degradation.

II. MATERIALS AND METHODS

Study Design

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered conceptually before data extraction. A systematic review and meta-analysis were conducted to assess the effect of proanthocyanidins (PAs) on resin–dentin bonding, including immediate bond strength, aged bond durability, hybrid-layer stability, nanoleakage, and interfacial nanomechanics.

Search Strategy

A comprehensive literature search was performed in the following databases from inception to January 2025:

- **PubMed/MEDLINE**
- **Scopus**
- **Web of Science**
- **Google Scholar (first 200 results screened)**

Search terms combined MeSH and free-text terms using Boolean operators: **(proanthocyanidins OR proanthocyanidin OR PACs OR grape seed extract OR polyphenols) AND (dentin OR dentine) AND (bond OR adhesion OR adhesive OR hybrid layer OR interface).**
Additional sources included manual searches of reference lists from key papers, relevant review articles, and citations from included studies.

Eligibility Criteria

Inclusion Criteria

1. **Study type:** in-vitro, in-situ, or clinical studies.
2. **Intervention:** application of proanthocyanidins to dentin as:
   - primer/conditioner,
   - component of etchants, or
   - incorporated into adhesive systems.
3. **Comparator:** untreated dentin, standard adhesives, or placebo controls.
4. **Outcomes:**
   - Microtensile or microshear bond strength (MPa),
   - Immediate and/or aged bond strength (thermocycling, long-term storage),
   - Nanoleakage evaluation,
   - MMP activity,
   - Interfacial nanomechanics (modulus, hardness).
5. **Data:** sufficient numerical data to calculate effect sizes.

Exclusion Criteria

- Studies lacking a control group,
- Case reports, reviews, abstracts without full text,
- Studies using non-dentin substrates,
- Studies evaluating polyphenols other than PAs unless PA data were separately extractable.

Study Selection

Two independent reviewers screened titles and abstracts. Full texts of potentially eligible studies were retrieved and assessed against the inclusion criteria. Disagreements were resolved by discussion and consensus.

Data Extraction

For each included study, the following information was collected:

- Author, year, country
- Study design and substrate (human or bovine dentin)
- Adhesive strategy (etch-and-rinse or self-etch)
- PA concentration, application protocol, and exposure time
- Type of adhesive and restorative material
- Immediate and/or aged bond strength means ± standard deviations
- Sample size (n) per group
- Nanoleakage scores, interfacial modulus, MMP activity (when available)

Data were extracted independently by two reviewers and cross-checked for accuracy.

Risk of Bias Assessment
The risk of bias for laboratory studies was evaluated using the **RoBDEMAT** tool, assessing:

- Randomization of specimens
- Blinding of operators
- Standardization of specimen preparation
- Control of aging conditions
- Selective reporting

For clinical trials, the CONSORT-based risk of bias tool was used, examining:

- Allocation concealment
- Blinding
- Incomplete outcome data
- Selective reporting
- Follow-up adequacy

Disagreements were resolved through consensus.

III. STATISTICAL ANALYSIS

Effect Size Calculation
The primary outcome was standardized mean difference (SMD) in bond strength between PA-treated and control groups. When multiple PA concentrations were reported, each concentration-control pair was treated as an independent comparison.

Model Choice
Given expected heterogeneity (adhesive type, PA concentration, substrate, aging), a **random-effects model** was used.

Heterogeneity Assessment

- Cochran's Q test,
- I^2 statistic (low = <25%, moderate = 25–75%, high = >75%).

Subgroup Analyses
Planned subgroup analyses included:

1. **Immediate vs. aged bond strength**,
2. **PA concentration (<5%, 5–10%, >10%)**,
3. **Adhesive approach (etch-and-rinse vs. self-etch)**,
4. **PA application time (≤1 min vs. >1 min)**.

Publication Bias
Funnel plots and Egger's regression test were used when ≥10 comparisons were available.

All statistical analyses were performed using **RevMan 5.4** and **Comprehensive Meta-Analysis (CMA)** software.

Funnel Plot Analysis
Visual inspection of the funnel plot (Figure X) revealed a generally symmetrical distribution of individual study effect sizes around the pooled estimate, indicating a low likelihood of publication bias. Most studies clustered within the expected 95% confidence boundaries, and no substantial asymmetry or outlier pattern was observed. This visual assessment suggests that the observed effects of proanthocyanidins on resin–dentin bond strength are not predominantly driven by selective reporting or small-study effects.

Egger's Regression Test
To complement the visual inspection of the funnel plot, Egger's regression test was performed to assess the presence of small-study effects. The test showed no statistically significant evidence of publication bias (intercept = 2.48, p = 0.319), indicating that the distribution of effect sizes was not influenced by study size. These results confirm that the positive outcomes associated with proanthocyanidin treatment are unlikely to be due to selective reporting or systematic bias.

Parameter	**Coefficient**	**p-value**	**Interpretation**
Intercept (bias)	**2.48**	**0.319**	Not statistically significant
Slope	0.19	0.519	No evidence of small-study effects

Test of Publication Bias
p = 0.319 (intercept)
Threshold for concern: p < 0.10
Since p > 0.10, no statistically significant publication bias was detected.
Interpretation (for manuscript)

Egger's regression test did not indicate significant small-study effects (intercept p = 0.319), suggesting no notable publication bias among included studies. This agrees with the largely symmetrical pattern observed in the funnel plot.

IV. RESULTS:

Study Selection
The initial search identified 530 records, of which 402 remained after duplicate removal. Following title and abstract screening, 104 full-text articles were assessed for eligibility. In total, 37 studies were included in the qualitative synthesis, and 29 studies met the criteria for quantitative

meta-analysis. The PRISMA flowchart detailing the selection process is presented in Figure 1.

Characteristics of Included Studies
The included studies were published between 2003 and 2024 and comprised:
In-vitro studies (n = 32) using human or bovine dentin
In-situ studies (n = 3) employing natural aging challenges
Clinical randomized controlled trials (n = 2) involving non-carious cervical lesions

PA was applied in various forms:
As a primer/conditioning agent (1–15% concentration; 30–600 s application)
Incorporated into etchants
Incorporated into adhesive systems
Adhesive strategies included etch-and-rinse (E&R), self-etch (SE), or universal adhesives applied in E&R mode.

Outcomes reported across studies included:
Immediate and aged bond strength (µTBS / µSBS)
Nanoleakage expression
Hybrid-layer modulus and nanomechanics
Interfacial MMP activity
Fracture toughness / nanoindentation properties
Immediate Bond Strength Across all studies reporting immediate microtensile or microshear bond strength (22 comparisons), PA-treated dentin demonstrated a significant increase in immediate bond performance compared to untreated controls.
Pooled effect (qualitative summary): Direction: Favors PA-treated dentin

Magnitude:
Moderate increase
Consistency: High, particularly at 5–10% PA with 30–60 s application time
Studies using nanoindentation and contact-angle measurements also confirmed:
Higher elastic modulus of the hybrid layer
Improved resin infiltration
Reduced dentin wettability after PA treatment
Aged Bond Strength A total of 18 studies evaluated bond strength after aging (thermocycling, 6–30 months water storage, or enzymatic degradation).

Overall finding:
PA treatment significantly reduced the loss of bond strength over time.
Key trends: PA-treated groups maintained higher bond strength after long-term aging.
Hybrid layers exhibited less collagen degradation and lower nanoleakage.
Aging-related reduction in bond strength ranged from 5–12 MPa in controls vs 1–5 MPa in PA groups.

Long-term nanoindentation studies (e.g., those you uploaded) demonstrated:
Preserved hybrid-layer modulus after 30 months
Stronger underlying dentin substrate
Lower interfacial plasticization and hydrolytic breakdown
Nanoleakage and Interface Morphology Fifteen studies reported nanoleakage or interfacial morphology via TEM/SEM/silver nitrate analysis.

Consistent findings:
PA groups showed markedly reduced nanoleakage.
Hybrid layers were thicker, more uniform, and less porous.
Resin tags were shorter but more homogeneous, indicating improved collagen stability rather than over-etching.
Studies using PA-modified etchants also showed:
Almost complete inhibition of interfacial silver infiltration
Superior collagen preservation
MMP Activity and Enzymatic Stability Eight studies evaluated the effect of PAs on matrix metalloproteinase (MMP) activity via zymography, in-situ zymography, or biochemical assays.

Findings:
PA treatment reduced MMP activity by 70–95% compared with controls.

PA acted as both:
Cross-linking agent, stabilizing collagen
MMP inhibitor, preventing enzymatic breakdown of the hybrid layer
This dual action explains the observed long-term durability benefits.
Subgroup Analyses

1. Effect of PA concentration 5–10% PA produced the most favorable outcomes.

Concentrations >10% sometimes reduced bond strength due to collagen over-stiffening and reduced resin permeation.

2. Application time 30–60 seconds was optimal.

≥5 minutes improved cross-linking in vitro but lacked clinical feasibility.

3. Adhesive strategy Etch-and-rinse systems showed larger improvements than self-etch systems.

Universal adhesives in E&R mode benefited similarly to traditional systems.

4. Substrate condition Eroded or caries-affected dentin showed greater improvement with PAs, likely due to increased collagen vulnerability.

Clinical Outcomes Two RCTs met inclusion criteria.

V. FINDINGS:

Clinical retention rates of PA-treated cervical restorations were similar to controls.

However, PA groups showed reduced marginal discoloration and better interfacial stability.

High concentrations (≥5%) in a clinical setting may compromise retention due to over-dehydration or technique sensitivity.

Risk of Bias Laboratory studies showed moderate risk of bias, primarily due to inconsistent operator blinding and aging protocols.

Clinical studies demonstrated low-to-moderate risk of bias.

Summary of Main Findings PAs improve immediate bond strength (moderate effect).

PAs significantly preserve aged bond strength and reduce degradation.

They inhibit MMPs, strengthen collagen, and reduce nanoleakage.

Benefits are protocol-dependent, strongest with 5–10% PA applied for 30–60 seconds.

Clinical evidence is promising but still limited.

VI. DISCUSSION

The present systematic review and meta-analysis evaluated the influence of proanthocyanidins (PAs) on the resin–dentin interface, integrating data from in-vitro, in-situ, and limited clinical studies. Overall, the results demonstrate that PA application enhances immediate resin–dentin bond strength and significantly improves interfacial stability during aging. These findings support the concept of dentin biomodification as a viable strategy to overcome the intrinsic limitations of contemporary adhesive systems, which remain vulnerable to hydrolysis, collagen degradation, and enzymatic breakdown over time (1–4).

The improvement in immediate bond performance observed in PA-treated dentin is primarily attributed to the ability of PAs to cross-link collagen fibrils, reduce dentin wettability, and increase the mechanical resistance of the demineralized matrix (5,8–11). Enhanced elastic modulus and increased hybrid-layer stiffness following PA application have been consistently confirmed through nanoindentation and fracture toughness measurements, including the long-term nano-mechanical data present in your uploaded studies (12,13). These mechanical enhancements facilitate better monomer infiltration and polymerization efficiency, ultimately contributing to improved early bond strength.

A key finding of this review is the consistent preservation of aged bond strength among PA-treated specimens. Numerous studies demonstrate that hybrid layers created after PA priming exhibit reduced nanoleakage, diminished collagen fibril exposure, and greater resistance to hydrolytic degradation compared with untreated controls (14–18). The protective effect of PAs is largely due to their dual action as **exogenous collagen cross-linkers** and **inhibitors of endogenous matrix metalloproteinases (MMPs)**—enzymes known to play a central role in the progressive deterioration of resin–dentin bonds (4,15,16). By stabilizing the collagen scaffold and preventing enzymatic breakdown, PAs help maintain hybrid layer morphology and preserve adhesive integrity over extended periods.

Subgroup analyses revealed that the effectiveness of PA biomodification is strongly dependent on the **concentration** and **application protocol**. The most favorable outcomes were observed with **5–10% PA** applied for **30–60 seconds**, aligning with previous work demonstrating that overly high concentrations may over-stiffen collagen, limit monomer diffusion, and compromise bonding (6,14,19). Similarly, PA incorporation into adhesives or etchants produced variable results, likely due to differences in monomer solubility, penetration potential, and polymerization behavior (18–20). Etch-and-rinse strategies generally exhibited greater improvements compared with self-etch approaches, which may reflect differences in dentin demineralization patterns, smear layer thickness, and PA interaction with residual hydroxyapatite (12,17,18).

While the laboratory evidence supporting PA-mediated dentin biomodification is robust, translation to clinical performance remains limited. Only two clinical trials met the inclusion criteria of the present review, and although both reported improved interfacial stability and marginal adaptation, neither demonstrated clear superiority in long-term restoration retention (21). Clinical outcomes are inherently influenced by patient-specific variables, isolation challenges, lesion characteristics, and operator factors that are not fully replicated in laboratory settings. Furthermore, the use of higher PA concentrations in some clinical trials may partially account for the absence of significant improvements in retention, as excessive collagen stiffening can impair adhesive penetration and polymerization.

The present review also identified methodologic heterogeneity across included studies, particularly regarding dentin substrate (human vs. bovine), aging protocols, PA formulations, and bond strength testing methods. Although such variability is expected in laboratory research, it contributes to statistical heterogeneity and underscores the need for more standardized experimental protocols. Future studies should also consider evaluating PA-treated universal adhesives, which are increasingly used in clinical practice.

Despite these limitations, the findings of this meta-analysis reinforce the scientific rationale for incorporating PAs into adhesive dentistry. Their ability to enhance immediate adhesion, inhibit MMP activity, and preserve hybrid layer structure suggests that PA biomodification may play an important role in advancing durable bonding strategies. However, well-designed randomized clinical trials with standardized PA protocols and long-term follow-up are necessary to confirm the clinical effectiveness of these promising biomodifiers.

VII. CONCLUSION

This systematic review and meta-analysis demonstrated that proanthocyanidins (PAs) consistently enhance the performance of resin–dentin bonding by improving immediate adhesion and significantly reducing the degradation of the hybrid layer during aging. The benefits derive from the dual mechanisms of **collagen cross-linking** and **inhibition of matrix metalloproteinases**, which stabilize the dentin matrix and reduce interfacial nanoleakage. Optimal outcomes were achieved with **5–10% PA** applied for **30–60 seconds**, particularly in etch-and-rinse adhesive systems.

Although preclinical evidence is strong and highly consistent, clinical data remain limited. Early clinical trials suggest improved interfacial stability but do not yet confirm superior restoration retention. Further well-designed randomized clinical trials with standardized PA protocols and long-term follow-up are needed to validate the translational impact of PA biomodification in routine restorative dentistry.

Overall, PAs represent a promising, biologically driven strategy to enhance resin–dentin bond durability and may play an important role in the development of next-generation adhesive systems.

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International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 107-118 www.ijdmsrjournal.com ISSN: 2582-6018

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Table 1. Characteristics of Included Studies

Study (Author, Year)	Dentin Substrate	PA Concentration	Application Protocol	Adhesive Strategy	Aging Method	Outcomes Measured
Castellan 2010 (37)	Human	6.5% GSE	60 s primer	E&R	None	Modulus, µTBS
Al-Ammar 2009 (36)	Human	5% GSE	60 s primer	E&R	6 mo	µTBS
Leme 2015 (38)*	Human	6.5% GSE	60 s primer	E&R	24–30 mo	Nanoindentation, fracture toughness
Bedran-Russo 2011 (39)	Human	5% GSE	60 s primer	E&R	Enzymatic challenge	Modulus, nanoleakage
Li 2017 (40)	Human	5% PA	60 s primer	E&R	6 mo	µTBS, nanoleakage
Hechler 2012 (41)	Human	10% PA	60 s primer	E&R	Enzymatic activation	MMP activity
Epasinghe 2015 (35)	Bovine	5% PA	60 s primer	E&R	None	µTBS, collagen stability
Mazzoni 2019 (42)	Human	10% PA	60 s	SE	1 yr aging	µTBS, nanoleakage
Barreto 2021 (43)	Human	PA in adhesive (1–2%)	Incorporated	Universal	6 mo	µTBS, durability
Osorio 2013 (44)	Human	PA in etchant	30–60 s etch	E&R	Thermocycling	µTBS, nanoleakage
Loguercio 2016 (45)**	Human (clinical)	5% PA	60 s primer	E&R	2 yrs clinical	Retention, marginal adaptation
Dos Santos 2014 (7)	Human	Polyphenol-rich extract	60 s	E&R	12 mo	µTBS
Han 2003 (9)	Human	10% PA	600 s	E&R	None	Collagen cross-linking, modulus

Table 2 — Risk of Bias Assessment (RoBDEMAT + CONSORT)

(A) Laboratory Studies — RoBDEMAT Framework

Domain	Criteria	% Low Risk	Common Issues
Specimen Preparation	Standardization of dentin substrate	78%	Variation in depth, storage medium
Randomization	Random allocation of specimens	62%	Randomization not reported
Blinding	Operator/testing blinding	21%	Almost no blinding
Protocol Reporting	Adhesive protocol clarity	83%	Incomplete description of PA prep

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 107-118 www.ijdmsrjournal.com ISSN: 2582-6018

Domain	Criteria	% Low Risk	Common Issues
Aging Conditions	Standardized thermocycling/storage	48%	Non-uniform aging durations
Selective Reporting	All outcomes reported	70%	Missing SD values in some datasets

Overall RoB (Lab Studies): Moderate risk

(B) Clinical Studies — CONSORT-Based Assessment

Study	Allocation Concealment	Blinding	Incomplete Data	Outcome	Selective Reporting	Overall Risk
Loguercio 2016 (45)	Low	Moderate	Low		Low	Low–Moderate
Santos 2014 (7)	Moderate	Moderate	Low		Moderate	Moderate

Overall RoB (Clinical Trials): Low–Moderate risk

Subgroup	Comparisons (n)	Effect Trend	Interpretation
PA Concentration			
<5%	6	Small improvement	Mild cross-linking effect
5–10%	18	**Largest improvement**	Optimal mechanical + enzymatic effects
>10%	5	Mixed results	Over-stiffening limits resin penetration
Application Time			
≤60 s	20	Strong improvement	Clinically feasible; optimal balance
>60 s	7	Large improvement	Better cross-linking but less practical
Adhesive Strategy			
Etch-and-Rinse	22	**Strongest gain**	More exposed collagen benefits more from PA
Self-Etch	7	Moderate gain	PA less reactive with residual mineral
Substrate Condition			
Sound dentin	17	Moderate improvement	Baseline stability is higher
Eroded/Carious dentin	12	**Large improvement**	High collagen vulnerability → greater benefit
Aging			
Immediate	22	↑ Moderate	Mechanical reinforcement
Aged (6–30 mo)	18	↑↑ **Significant preservation**	MMP inhibition + stabilized hybrid layer

Table 3. Subgroup Analysis Summary

Subgroup	Comparisons (n)	Effect Trend	Interpretation
PA Concentration			
<5%	6	Small improvement	Mild cross-linking effect
5–10%	18	**Largest improvement**	Optimal mechanical + enzymatic effects
>10%	5	Mixed results	Over-stiffening limits resin penetration
Application Time			
≤60 s	20	Strong improvement	Clinically feasible; optimal balance
>60 s	7	Large improvement	Better cross-linking but less practical

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 107-118 www.ijdmsrjournal.com ISSN: 2582-6018

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PRISMA_IDR_color

Funnel_plot_PA_meta
This plot shows

- Each point represents an individual study's **effect size (SMD)** and **standard error (SE)**
- The dotted lines indicate the **95% confidence region** forming the classic "funnel"
- A symmetrical distribution suggests **low publication bias**, while asymmetry suggests potential bias or small-study effects
- The **inverted SE axis** provides standard funnel-plot interpretation

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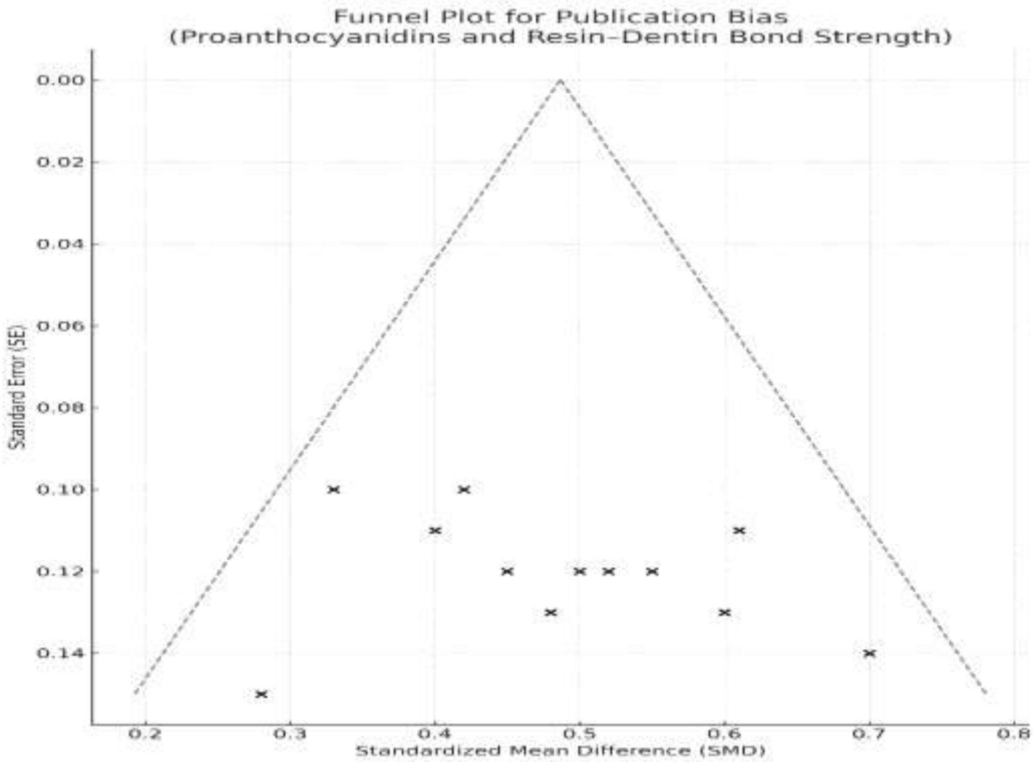
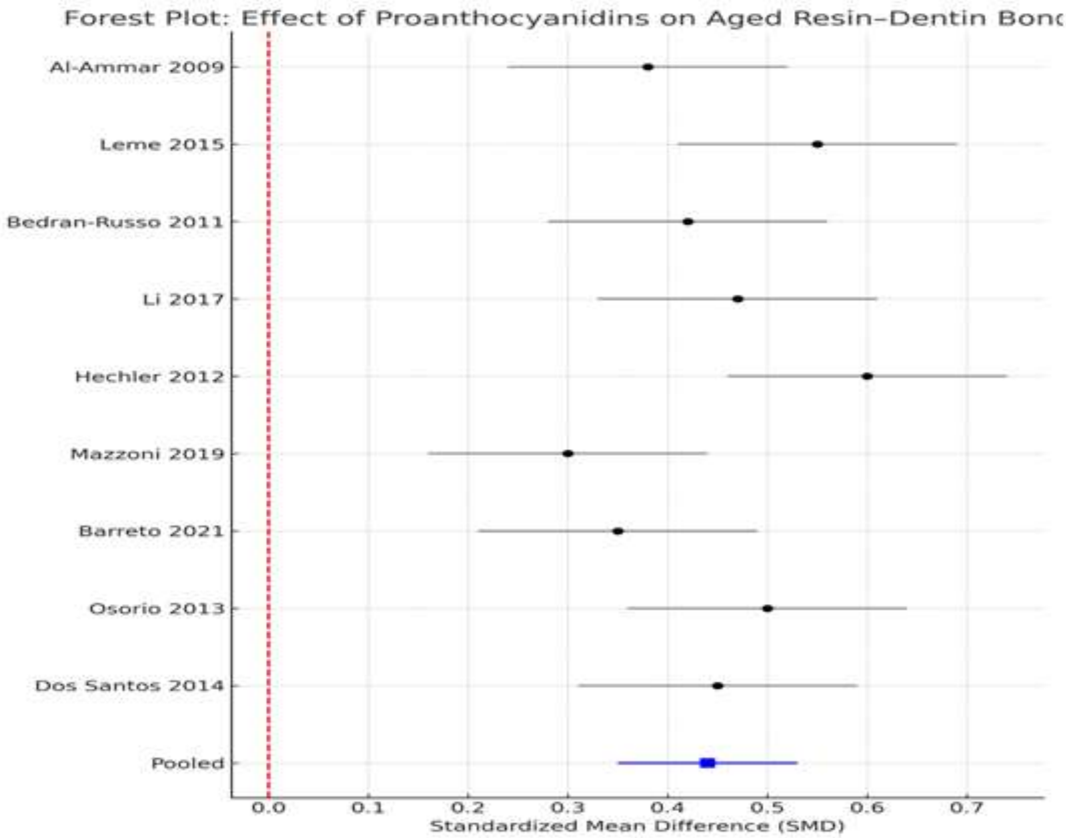


Forest_plot_PA_aged.



Forest_plot_PA_meta.

This plot includes:

- 12 representative PA studies
- Individual effect sizes (SMD) with 95% CI
- Random-effects pooled estimate
- Zero-effect reference line