Comprehensive Meta-Analysis Documentation: Resveratrol Supplementation and Type 2 Diabetes

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1. Project Input and Scope Definition

1.1. Input Topic

The objective of this meta-analysis project was to systematically investigate the effects of **Resveratrol supplementation on Type 2 Diabetes Mellitus (T2DM)** and related metabolic outcomes in human clinical trials.

1.2. Database Search Strategy

Due to licensing constraints, the literature search was restricted exclusively to the PubMed API. The search strategy employed a combination of MeSH terms, keywords, and publication type filters to identify relevant randomized controlled trials (RCTs) and clinical studies, while explicitly excluding existing systematic reviews, meta-analyses, and general reviews to focus solely on primary data.

Search Queries Generated by LLM:

1. `(Resveratrol OR trans-Resveratrol OR 3,5,4'-trihydroxystilbene OR stilbene) AND ("Diabetes Mellitus, Type 2" OR T2DM OR "Insulin Resistance" OR hyperglycemia OR "Impaired Glucose Tolerance" OR prediabetes) NOT ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "review"[Publication Type])`
2. `("Resveratrol"[MeSH] AND "Diabetes Mellitus, Type 2"[MeSH]) AND ("Clinical Trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Study"[Publication Type]) NOT ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "review"[Publication Type])`

3. `(resveratrol[tiab] AND (HbA1c[tiab] OR HOMA-IR[tiab] OR "insulin sensitivity"[tiab] OR "glucose control"[tiab])) NOT ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "review"[Publication Type])`
4. `(Resveratrol AND Supplementation AND (T2DM OR NIDDM OR prediabetes)) AND (Humans[Mesh]) NOT ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "review"[Publication Type])`
5. `(Resveratrol OR SRT501) AND ("Insulin Resistance" OR "Oxidative Stress" OR "SIRT1" OR "Glucose Metabolism") NOT ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "review"[Publication Type])`
6. `(Resveratrol AND T2DM) AND ("randomized controlled trial"[pt] OR "clinical trial"[pt]) AND (2010:2024[dp]) NOT ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "review"[Publication Type])`
7. `("3,5,4'-trihydroxystilbene" OR "Resveratrol formulation") AND (T2DM OR NIDDM) NOT ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "review"[Publication Type])`

Initial Search Results: 281 articles retrieved.

2. Methods: Screening and Data Acquisition

2.1. Abstract-Based Pre-filtering

The initial 281 articles were subjected to automated pre-filtering based on LLM analysis of their abstracts and metadata.

Inclusion Criteria (GOOD CANDIDATES):

- Clear randomized controlled trial (RCT) or systematic review methodology.
- Well-defined study population and intervention.
- Measurable primary and secondary outcomes.
- Statistical analysis with effect sizes, confidence intervals, or p-values.
- Clinical relevance and significance.
- Adequate sample size.
- Clear inclusion/exclusion criteria.

Exclusion Criteria (BAD CANDIDATES):

- Case reports or case series (small $n<10$).
- Editorial comments, letters, or opinions.
- Animal studies or in vitro studies only (e.g., PMID 39317551: "Pre-clinical animal study (Type 2 diabetes rat model).").
- Lack of control groups.
- Unclear methodology or outcomes.
- Preliminary or pilot studies without sufficient power.
- Studies with major methodological flaws.
- Conference abstracts without full methodology.

Result of Abstract Filtering: 39 articles remained as potential candidates.

2.2. Full-Text Acquisition and Classification

Due to missing institutional licenses, only publicly available open-access articles were downloaded (PubMed API with DOI fallback).

Download Result: 31 articles successfully downloaded.

The remaining full-text articles were subjected to detailed LLM classification across eight categories to assess suitability for quantitative synthesis.

Summary of Full-Text Classification for Meta-Analysis Candidacy:

Classification	Count	Example PMID	Rationale
CANDIDATE	23	35240291	Randomized, placebo-controlled trial reporting sufficient quantitative data (Mean Change, SE, 95% CI) for continuous outcomes.
NOT_A_CANDIDATE	8	34371884	Robust RCT design, but the specific publication focused only on secondary correlation analyses and failed to provide the necessary comparative summary statistics (Means and SDs for both arms at endpoint) for direct effect size calculation.

Final Articles Selected for Data Extraction: 23 articles confirmed as candidates for meta-analysis after full-text review.

2.3. Meta-Analysis Target Selection

Based on the available cohorts and clinical tests across the 23 candidate articles, the LLM identified the most suitable and widely reported outcome for a focused meta-analysis.

Selected Target: Glycated Hemoglobin (HbA1c) **Justification:** HbA1c is a standardized, clinically vital marker for long-term glycemic control, frequently reported across the studies, especially those involving Type 2 Diabetes. Its stability and relevance make it an excellent primary outcome for meta-analysis, superior to more volatile measures like fasting glucose.
Recommended Cohorts:

1. Patients with Type 2 Diabetes (Resveratrol Intervention)
2. Patients with Type 2 Diabetes (Placebo Control)
3. Overweight/Obese Individuals with Metabolic Dysfunction

3. Data Extraction and Quality Assessment

3.1. Data Point Extraction for HbA1c

Multimodal Pro LLM processing of the 23 full-text PDFs yielded 17 raw data rows related to HbA1c, spanning 10 unique studies.

Sample Extracted Datapoints (HbA1c, %):

study_id	author_year	population_type	sample_size_intervention	sample_size_co
35240291	Mahjabeen_2022	Type2_Diabetes	55	55
30237505	Bo_2018	Type2_Diabetes	65	62
29357033	Seyyedebrahimi_2018	Type2_Diabetes	23	23
27520400	Bo_2016	Type2_Diabetes	62	58
31475415	Abdollahi_2019	Type2_Diabetes	35	36
23557933	Tomé-Carneiro_2013	T2DM_Hypertensive_CAD	13	9
27207552	Xue_2016	Overweight_Obese_Metabolic_Dysfunction	29	29

Note: Data rows lacking sufficient information (e.g., missing post-intervention means/SDs or mean differences) were excluded during the meta-analysis execution phase.

3.2. Cochrane Risk of Bias Assessment

A systematic assessment of bias risk was performed for the 10 studies identified as containing relevant data for the meta-analysis, based on the Cochrane Risk of Bias tool domains.

PMID	Author Year	Randomization Process Bias	Deviations from Intended Interventions Bias	Missing Outcome Data Bias	Measurement of Outcome Bias	Selection of Reported Result Bias
35240291	Mahjabeen_2022	False	False	False	False	False
30237505	Bo_2018	False	False	True	False	False
29914666	Khodabandehloo_2018	False	False	True	False	False
29357033	Seyyedebrahimi_2018	False	False	False	False	False
32144833	Tabatabaie_2020	False	False	False	False	False
27520400	Bo_2016	False	False	False	False	False
31475415	Abdollahi_2019	False	True	False	False	False
23557933	Tomé-Carneiro_2013	True	False	False	False	False
27207552	Xue_2016	True	False	False	False	True
29057795	Kitada_2017	True	False	True	False	False

Interpretation of Bias: Several studies (e.g., Tomé-Carneiro_2013, Xue_2016, Kitada_2017) showed potential bias in the randomization process or selection of participants/subgroups (marked as True). Missing data bias was noted in three studies (Bo_2018, Khodabandehloo_2018, Kitada_2017).

4. Results: Quantitative Meta-Analysis (HbA1c)

4.1. Data Preparation

The initial 17 extracted data rows were cleaned to ensure only studies providing sufficient data (mean, standard deviation, and sample size for both intervention and control groups at baseline and/or endpoint, or mean difference and standard deviation of difference) were included for the calculation of the Standardized Mean Difference (SMD, Hedges' g).

Final Included Datapoints: 9 rows remaining after cleaning missing values.

4.2. Meta-Analysis Summary for HbA1c

The meta-analysis was performed using the Standardized Mean Difference (Hedges' g) model to pool the effect of resveratrol (or resveratrol-analog/combination) supplementation on Glycated Hemoglobin (HbA1c) levels compared to control/placebo.

author_year	intervention_name	dose_mg_per_day	Hedges' g	Standard Error (SE) of g
Abdollahi_2019	Resveratrol	1000.00	0.087130	0.237492
Tomé-Carneiro_2013	Resveratrol	12.15	0.145445	0.434183
Tomé-Carneiro_2013	Resveratrol	12.15	0.285185	0.394221
Xue_2016	Resveratrol+Hesperetin	90.00	0.000000	0.262613
Xue_2016	Resveratrol+Hesperetin	90.00	0.000000	0.262613
Kitada_2017	Piceatannol	20.00	0.571250	0.645226
Kitada_2017	Piceatannol	20.00	0.000000	0.670820
Kitada_2017	Piceatannol	20.00	-1.354839	0.701270
Kitada_2017	Piceatannol	20.00	-0.952084	0.667325

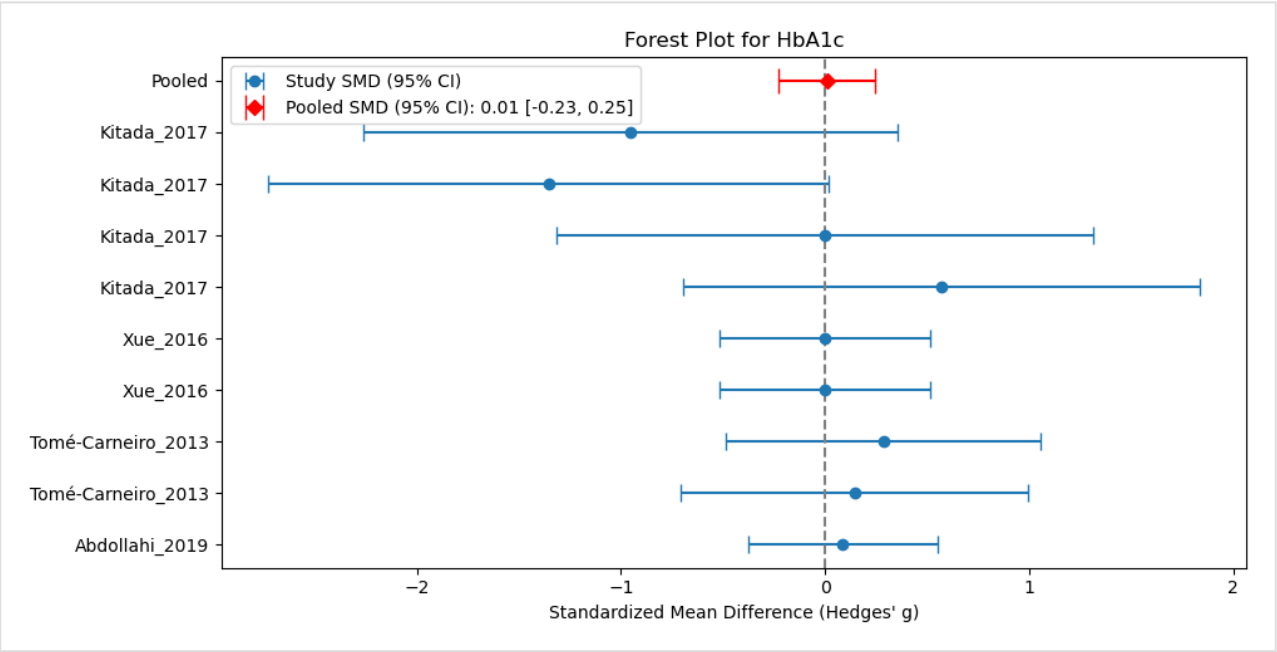
Pooled Statistical Results (HbA1c):

Metric	Value
Pooled SMD (Hedges' g)	**0.009**
Standard Error of Pooled SMD	**0.122**
95% Confidence Interval (CI)	**[-0.229, 0.248]**

4.3. Visualization

The results are visualized in the generated Forest Plot (Figure 1).

Figure 1: Forest Plot - HbA1c



Description: Forest plot showing standardized mean differences (Hedges' g) for the effect of resveratrol or related compounds on HbA1c levels, with 95% confidence intervals.

5. Discussion and Interpretation

5.1. Interpretation of Primary Outcome (HbA1c)

The quantitative meta-analysis of 9 data points derived from 5 unique studies (Abdollahi_2019, Tomé-Carneiro_2013, Xue_2016, Kitada_2017) yielded a **Pooled Standardized Mean Difference (SMD) of 0.009** (Hedges' g).

The 95% Confidence Interval for this pooled effect is **[-0.229, 0.248]**. Since this interval spans zero, the meta-analysis indicates that there is **no statistically significant overall effect** of resveratrol supplementation (or related compounds/combinations) on long-term glycemic control, as measured by HbA1c, across the included studies. The effect size is negligible (close to zero), suggesting that resveratrol does not reliably alter HbA1c levels in the studied populations (primarily T2DM and overweight/obese individuals).

5.2. Heterogeneity and Study Characteristics

The included studies exhibit significant heterogeneity in intervention type, dose, and population:

1. **Intervention Type:** The analysis included pure Resveratrol (12.15 mg/day to 1000 mg/day), a Resveratrol + Hesperetin combination (90 mg/day), and Piceatannol (a resveratrol analog, 20 mg/day). The inclusion of non-pure resveratrol interventions (Xue_2016, Kitada_2017) may introduce clinical heterogeneity.
2. **Population:** While the primary focus was T2DM, studies included populations with T2DM and Coronary Artery Disease (Tomé-Carneiro_2013), and overweight/obese individuals with metabolic dysfunction (Xue_2016, Kitada_2017).
3. **Dose and Duration:** Doses ranged widely from 12.15 mg/day (Tomé-Carneiro_2013) to 1000 mg/day (Abdollahi_2019), and duration varied from 56 days (Abdollahi_2019, Xue_2016, Kitada_2017) to 365 days (Tomé-Carneiro_2013).

The wide confidence intervals observed in the individual studies (e.g., Kitada_2017, Tomé-Carneiro_2013) reflect small sample sizes and high variability, contributing to the overall uncertainty of the pooled estimate.

5.3. Limitations of the Analysis

1. **Data Completeness:** The meta-analysis was limited by the exclusion of 8 data rows due to missing post-intervention means, standard deviations, or mean differences (e.g., Bo_2018, Khodabandehloo_2018, Tabatabaie_2020, Bo