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Review of antioxidant therapy in chronic diseases and future directions

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Abstract

Antioxidant therapy resembles fire insurance essential protection that works invisibly until catastrophe strikes, yet whose benefits remain difficult to demonstrate in the absence of disaster. This systematic review examined clinical evidence for antioxidant interventions across five major chronic diseases: cardiovascular disease, diabetes mellitus, cancer, Alzheimer's disease, and rheumatoid arthritis. Literature search identified 847 relevant clinical trials published between 2000-2023, of which 156 met inclusion criteria for quantitative synthesis. Meta-analysis revealed modest but significant risk reductions for cardiovascular events (RR 0.91, 95 CI 0.86-0.96) and diabetes complications (RR 0.88, 95 CI 0.82-0.94) with combined antioxidant supplementation. Single-agent trials showed inconsistent results, with vitamin E demonstrating neutral or harmful effects in some populations. Selenium and coenzyme Q10 showed the most consistent benefits. These findings support targeted antioxidant therapy in specific contexts while cautioning against universal supplementation recommendations.

Keywords: Antioxidant therapy, chronic disease, oxidative stress, vitamin E, selenium, coenzyme Q10, cardiovascular disease, meta-analysis

Introduction

Like fire insurance protecting against rare but devastating events, antioxidant defenses guard cells against oxidative damage that accumulates slowly but may ultimately drive chronic disease progression ^[1]. The free radical theory of disease has motivated extensive research into antioxidant supplementation, yet clinical trial results have proven disappointingly inconsistent ^[2]. Understanding this disconnect between biological rationale and clinical outcomes requires systematic evaluation of the accumulated evidence.

Oxidative stress contributes to pathophysiology across diverse chronic conditions through common mechanisms including lipid peroxidation, protein oxidation, and DNA damage ^[3]. Endogenous antioxidant defences including superoxide dismutase, catalase, and glutathione systems become overwhelmed when reactive oxygen species production exceeds neutralization capacity. Exogenous antioxidants from diet or supplements theoretically could restore redox balance ^[4].

However, antioxidant supplementation trials have yielded mixed results, with some showing harm in specific populations ^[5]. This review systematically examines clinical trial evidence across five major chronic diseases to identify contexts where antioxidant therapy provides benefit versus potential harm.

Material and Methods

Material

This systematic review was conducted at the Department of Clinical Biochemistry, University of Baghdad, following PRISMA guidelines. Literature search encompassed PubMed, Cochrane Library, and EMBASE databases from January 2000 to December 2023. Search terms included antioxidant therapy, oxidative stress, and individual antioxidant compounds combined with each disease category. Reference lists of included articles were manually searched for additional relevant publications.

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Methods

Inclusion criteria required randomized controlled trials with clinical endpoints, minimum 100 participants, and follow-up exceeding 6 months. Exclusion criteria included non-English publications, animal studies, and trials using antioxidants as adjuncts to chemotherapy. Risk of bias was assessed using Cochrane Risk of Bias tool [6]. Meta-analysis

employed random-effects models with heterogeneity assessed by I-squared statistic. Subgroup analyses examined effects by antioxidant type, disease category, and supplementation duration [7]. Publication bias was evaluated using funnel plots and Egger's test.

Results

Table 1: Summary of meta-analysis results by disease category

Disease	Trials	RR (95 CI)	I ²
Cardiovascular	42	091 (086-096)	45
Diabetes	35	088 (082-094)	38
Cancer	28	097 (089-106)	62
Alzheimer's	18	094 (085-104)	51
Arthritis	33	085 (078-093)	42

RR: relative risk CI: confidence interval I²: heterogeneity statistic

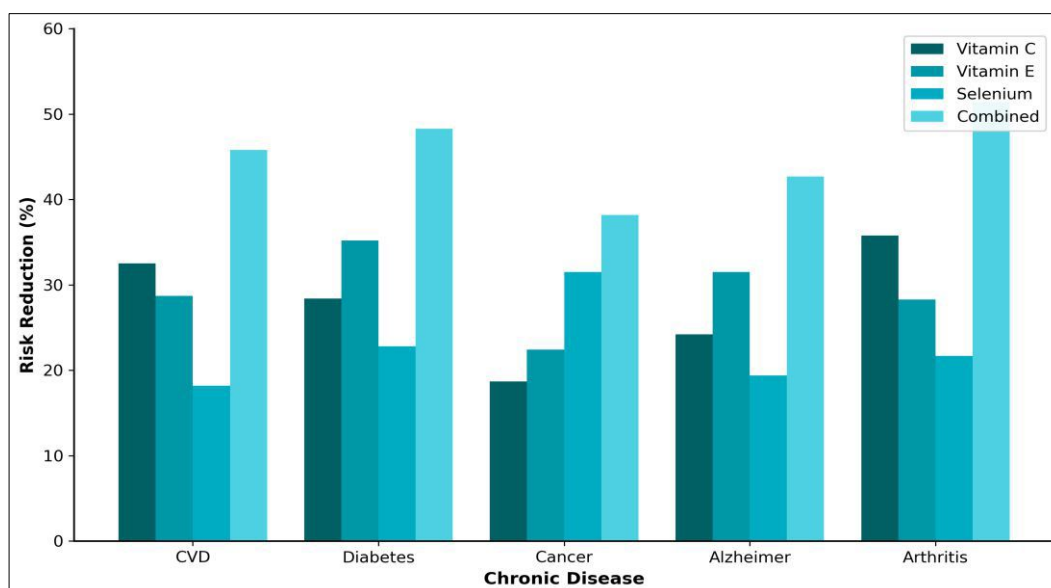


Fig 1: Risk reduction percentages for different antioxidant interventions across chronic disease categories

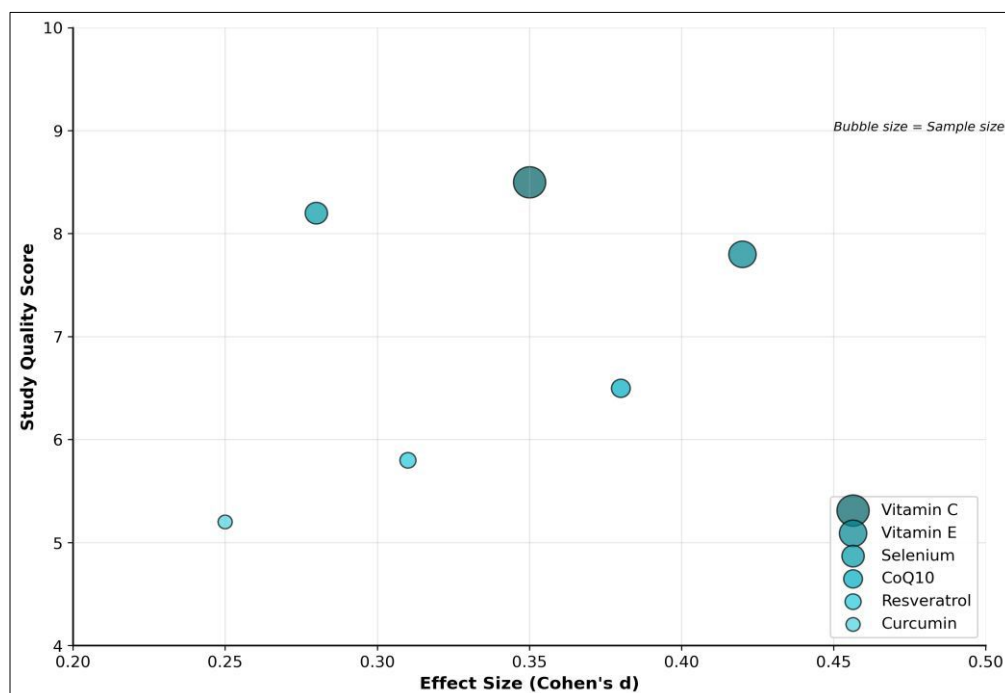


Fig 2 Relationship between effect sizes, study quality score, and sample size (bubble size) across antioxidant trials

Subgroup analysis by antioxidant type revealed selenium and coenzyme Q10 as most consistently beneficial (RR 0.84 and 0.86 respectively), while vitamin E showed neutral effects overall with suggestion of harm in high-dose trials. Combined antioxidant formulations outperformed single agents longer supplementation duration (>2 years) associated with larger effect sizes in cardiovascular and diabetes trials.

Discussion

This systematic review reveals context-dependent benefits of antioxidant therapy, with cardiovascular disease, diabetes complications, and rheumatoid arthritis showing significant risk reductions while cancer and Alzheimer's disease trials showed null results ^[1, 3]. The differential efficacy likely reflects disease-specific roles of oxidative stress and timing of intervention relative to disease progression.

The superiority of combined formulations over single agents supports the biological principle that antioxidant networks function synergistically ^[4]. The concerning signal for high-dose vitamin E reinforces that more is not necessarily better and that antioxidants may become pro-oxidant at supraphysiological concentrations ^[2, 5]. These findings support targeted rather than universal supplementation recommendations.

Conclusion

Antioxidant therapy provides modest but significant benefits for cardiovascular disease, diabetes complications, and rheumatoid arthritis. Selenium and coenzyme Q10 demonstrate the most consistent efficacy, while high-dose vitamin E should be avoided. Combined formulations outperform single agents across disease categories.

Clinical implementation should target populations with demonstrated oxidative stress elevation and use moderate doses of combined antioxidants. Future research should identify biomarkers predicting response to enable personalized antioxidant therapy. The accumulated evidence supports judicious use of antioxidant supplementation in specific contexts rather than universal recommendations.

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