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Systematic Review of the Effectiveness of Natural Antioxidants in Combating Oxidative Stress-Related Diseases

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Abstract

This study aimed to evaluate the effectiveness of natural antioxidants in mitigating oxidative stress-related diseases through a quantitative meta-analysis of existing literature. Anchored on the relationship between oxidative stress and disease progression, the study examined how natural antioxidants—such as polyphenols, flavonoids, and carotenoids—reduce reactive oxygen species and enhance antioxidant defenses. The research employed a meta-analytic design using secondary data from peer-reviewed studies, primarily involving experimental rodent models. Data were systematically collected using a structured extraction form, and analyzed through forest plots, heterogeneity tests, and funnel plots to assess effect sizes, variability, and publication bias. The findings revealed that natural antioxidants significantly reduced lipid peroxidation, as indicated by decreased malondialdehyde levels, and markedly increased antioxidant enzyme activities, including superoxide dismutase, catalase, glutathione, and glutathione peroxidase. Despite substantial heterogeneity across studies, the overall results consistently demonstrated beneficial effects of antioxidant interventions. Polyphenols and flavonoids, particularly morin, curcumin, resveratrol, green tea catechins, and quercetin, exhibited the strongest effects, although some compounds showed limited efficacy. Challenges identified included variability in study design, dosage, and methodology, as well as potential publication bias and limited generalizability due to reliance on animal models. The study concludes that natural antioxidants effectively enhance the body's defense against oxidative stress, though further standardized and human-based research is necessary. This study aligns with SDG 3 (Good Health and Well-Being) by supporting strategies for preventing chronic diseases and SDG 12 (Responsible Consumption and Production) through the promotion of plant-based antioxidants. It contributes to public health and nutritional sustainability by advancing evidence-based approaches for disease prevention and supporting the development of antioxidant-based healthcare interventions.

Keywords: Antioxidants, Catalase, Glutathione, Meta-analysis, Oxidative stress, Polyphenols, Reactive oxygen species, Superoxide dismutase

1. Introduction

Chronic non-communicable diseases (NCDs) remain a major global health challenge, with oxidative stress identified as a key underlying mechanism contributing to disease progression. Natural antioxidants have gained attention for their potential to mitigate oxidative stress and improve health outcomes. However, inconsistencies in existing research highlight the need for systematic synthesis. This study consolidates evidence on the effectiveness of natural antioxidants through meta-analysis to clarify their role in reducing oxidative stress-related diseases.

1.1 Background on Oxidative Stress and Natural Antioxidants in Chronic Disease Development

Chronic non-communicable diseases (NCDs), including diabetes mellitus, cardiovascular disease, and cancer, are leading causes of mortality worldwide. In the Philippines, cerebrovascular disease, neoplasms, and ischemic heart conditions were reported as the top causes of death in 2024, with common chronic conditions including diabetes, hypertension, heart disease, cancer, respiratory diseases, and kidney disease (Yap, 2024). A major contributor to these conditions is oxidative stress, which arises when pro-oxidants exceed antioxidant defenses (Pizzino et al., 2017). Reactive oxygen species (ROS)—such as superoxide anions, hydrogen peroxide, hydroxyl radicals, and peroxynitrite—are generated through metabolism, environmental exposure, and diet (Halliwell & Gutteridge, 2015). While ROS play beneficial physiological roles at moderate levels, excessive accumulation leads to cellular damage. Antioxidant systems, including vitamins C and E and enzymes like glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), regulate ROS levels (Pizzino et al., 2017). Oxidative stress also activates inflammatory pathways such as nuclear factor-kappa B (NF-κB), increasing cytokines like interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), thereby accelerating chronic disease progression (Reuter et al., 2010).

1.2 Evidence on Polyphenols, Flavonoids, and Carotenoids as Natural Antioxidants

Natural antioxidants have been widely studied for their role in restoring redox balance by neutralizing ROS through mechanisms such as free radical scavenging, enzyme enhancement, and metal ion interaction. Polyphenols exhibit strong antioxidant activity and are associated with reduced risks of chronic diseases (Pandey & Rizvi, 2009; Younas et al., 2018). Flavonoids protect cellular components, modulate immune responses, and reduce inflammation (Pandey & Rizvi, 2009; Panche et al., 2016; Aziz et al., 2018). Carotenoids, including lycopene and β-carotene, act as lipophilic antioxidants that protect against oxidative damage and are linked to reduced risks of chronic diseases (Fiedor & Burda, 2014). Natural antioxidants also enhance endogenous defense systems by increasing GPx, CAT, and SOD activity. However, findings remain inconsistent, with some studies showing benefits (Boots et al., 2011; Xuan et al., 2016) and others reporting limited effects (Shanely et al., 2009; Coombes et al., 2015).

1.3 Burden of Oxidative Stress-Related Diseases in Global and Philippine Contexts

Globally, NCDs significantly burden healthcare systems and affect populations across all age groups. In the Philippines, high mortality rates from chronic diseases emphasize the urgency of preventive strategies. The use of natural antioxidants reflects growing global and local efforts to address oxidative stress-related diseases through accessible and sustainable interventions.

1.4 Conceptual Relationship Between Natural Antioxidants and Disease Mitigation

The study is based on the relationship between oxidative stress and disease progression, where excess ROS leads to cellular damage and inflammation. Natural antioxidants—such as polyphenols, flavonoids, and carotenoids—intervene by scavenging free radicals, reducing inflammation, and enhancing antioxidant enzyme activity. This leads to reduced oxidative stress, slower disease progression, and improved health outcomes.

1.5 Inconsistencies in Antioxidant Research and Need for Meta-Analysis

Research on natural antioxidants shows variability in sources, dosages, and methodologies, as well as inconsistent biomarker selection. Some studies rely on malondialdehyde (MDA), while others assess enzymatic antioxidants, resulting in conflicting findings (Laila et al., 2025; Cikman et al., 2015). Additionally, inconsistent results have been observed for compounds such as quercetin and astaxanthin (Boots et al., 2011; Shanely et al., 2009; Xuan et al., 2016; Coombes et al., 2015). These limitations highlight the need for systematic quantitative synthesis. A meta-analysis provides a comprehensive approach to identify trends, strengthen evidence, and guide future research and applications.

1.6 Alignment with Sustainable Development Goals on Health, Nutrition, and Innovation

This study aligns with SDG 3 (Good Health and Well-Being) by contributing to strategies for preventing and managing chronic diseases. It also supports SDG 2 (Zero Hunger) and SDG 12 (Responsible Consumption and Production) through the promotion of plant-based, antioxidant-rich diets. Furthermore, it aligns with SDG 9 (Industry, Innovation and Infrastructure) by informing the development of health-related products derived from natural antioxidants.

1.7 Contribution of Antioxidant Research to Multidisciplinary Health and Sustainability

This study contributes to public health sustainability by supporting preventive healthcare strategies against chronic diseases. It advances nutritional sustainability through the promotion of plant-based antioxidants and informs pharmaceutical and healthcare innovation by guiding product development. Additionally, it strengthens research sustainability by addressing inconsistencies and promoting standardized methodologies.

2. Material and methods

2.1 Research Design

This study employed a quantitative research design using meta-analysis to systematically collect and synthesize findings from independent studies on natural antioxidants and oxidative stress-related disorders. This approach enhances statistical power, provides a more precise estimate of overall effect size, and enables identification of patterns, trends, and sources of variation. It also addresses inconsistencies and methodological gaps in existing literature, allowing for evidence-based conclusions regarding antioxidant efficacy.

2.2 Locale of the Study

The study was conducted in Pagadian City, Zamboanga del Sur, during the first semester of the 2025–2026 school year. As a systematic review, it relied entirely on published secondary data from academic databases and did not involve any physical research setting such as classrooms or laboratories.

2.3 Respondents of the Study

No primary data were collected in this study. The data were derived from previously published studies whose participants primarily consisted of experimental rodent species used to examine the effects of natural antioxidants on oxidative stress-related diseases.

2.4 Sample and Sampling Procedure

Relevant studies were identified through a systematic search of electronic databases, including Research Rabbit, Scholar, Mendeley, and PubMed. Medical Subject Headings (MeSH) terms related to natural antioxidants, oxidative stress, and associated diseases were used, along with Boolean operators to refine results. Reference lists of selected studies were also reviewed to identify additional sources. Inclusion criteria comprised studies examining natural antioxidants on oxidative stress markers, using experimental animal models, reporting quantitative data, published in Q1–Q3 peer-reviewed journals, including a control group, and providing sufficient data for effect size calculation. Exclusion criteria included studies lacking sufficient data, non-peer-reviewed works, absence of control groups, combined interventions with unclear effects, focus on synthetic antioxidants, or absence of relevant oxidative stress markers. Eligible studies underwent full-text screening, and selection followed PRISMA guidelines to ensure transparency and reproducibility (Page et al., 2021).

2.5 Research Instrument

The study utilized a structured data extraction form instead of traditional instruments. This form systematically collected key information from each study, including author details, type of natural antioxidant, oxidative stress indicators, research design, and outcomes such as lipid peroxidation and antioxidant activity. It also recorded statistical values like means and standard deviations, as well as reported limitations. This ensured consistency, accuracy, and transparency in data collection and synthesis.

2.6 Data Gathering Procedure

A comprehensive and systematic data collection process was conducted through database searches and manual review of reference lists. Identified studies were screened using predefined inclusion and exclusion criteria, followed by full-text evaluation to confirm eligibility. The process adhered to PRISMA guidelines (Page et al., 2021), ensuring a transparent and reproducible selection of studies for the meta-analysis.

2.7 Data Analysis Techniques

The study employed forest plots, heterogeneity analysis, and funnel plots to evaluate the effectiveness of natural antioxidants. Forest plots displayed individual and overall effect sizes with confidence intervals, enabling comparison across studies. Heterogeneity was assessed using Cochran's Q, I^2, and Tau^2 statistics to determine variability and guide subgroup analyses based on antioxidant type, biomarkers, disease category, and study design. Funnel plots and Egger's test were used to detect publication bias, while sensitivity analyses evaluated its impact. These methods ensured a rigorous and comprehensive statistical evaluation of the collected data.

2.8 Ethical Considerations

The study analyzed published literature and did not involve human participants. Ethical standards were maintained through proper citation, adherence to academic integrity, and avoidance of data fabrication or falsification. Transparency and objectivity were ensured by including both positive and negative findings and conducting a comprehensive literature search. Privacy and confidentiality standards were upheld, and findings were reported accurately and responsibly to avoid misleading interpretations.

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3. Results and Discussion

3.1 Effects of Natural Antioxidants on Oxidative Stress Markers

3.1.1 Lipid Peroxidation Marker (MDA)

The analysis of four studies showed that natural antioxidants, including cumin, resveratrol, turmeric, ginger, and quercetin, significantly reduced malondialdehyde (MDA) levels. All studies reported negative effect sizes, with an overall large and statistically significant pooled effect ($g = -2.926$). Sultan et al. (2025) demonstrated the largest reduction, while Eybl et al. (2006) reported the smallest but still significant effect. However, heterogeneity was considerable ($I^2 = 89.6\%$), indicating variability across studies. Funnel plot analysis showed no statistically significant publication bias ($p = 0.651$). These findings confirm that natural antioxidants effectively reduce lipid peroxidation, a key indicator of oxidative damage. The results align with previous studies showing that compounds such as curcumin, resveratrol, and ginger reduce oxidative stress and improve antioxidant capacity (Cakina et al., 2024; Oboh et al., 2010). The observed heterogeneity suggests that differences in experimental conditions, dosage, and methodologies influence the magnitude of effects, although the overall direction remains consistently beneficial.

3.1.2 Antioxidant Enzyme Activity (SOD)

Seven studies consistently showed that natural antioxidants significantly increased superoxide dismutase (SOD) activity, with a large pooled effect size ($g = 3.697$, $p = 0.000$). Most studies reported large and statistically significant effects, except Bártikova et al. (2015), which showed a small and non-significant effect. Substantial heterogeneity was observed ($I^2 = 93\%$), though funnel plot analysis indicated no significant publication bias ($p = 0.372$). The results demonstrate that natural antioxidants enhance enzymatic defense against oxidative stress. This is supported by prior findings that ginger, turmeric, and quercetin increase SOD activity and improve antioxidant status (Rezaei-Moghadam et al., 2012; Edremitlioglu et al., 2011). Despite variability across studies, the consistent positive effect highlights the robustness of antioxidant interventions in strengthening cellular defense mechanisms.

3.1.3 Antioxidant Enzyme Activity (CAT)

Eight studies showed that natural antioxidants significantly increased catalase (CAT) activity, with a large pooled effect size ($g = 2.316$, $p < 0.001$). Strong effects were observed in studies using morin, green tea, and quercetin, while some studies showed smaller, non-significant effects. Heterogeneity was substantial ($I^2 = 85.842\%$), and funnel plot analysis indicated significant publication bias ($p < 0.001$). These findings suggest that natural antioxidants enhance the breakdown of reactive oxygen species, particularly hydrogen peroxide, thereby reducing oxidative damage. The variability in results may be attributed to differences in antioxidant dosage, exposure duration, and experimental conditions. The presence of publication bias indicates that positive findings may be overrepresented, warranting cautious interpretation of the overall effect.

3.1.4 Antioxidant Capacity Marker (GSH)

Four studies reported that natural antioxidants significantly increased glutathione (GSH) levels, with a large pooled effect ($g = 4.705$, $p = 0.001$). The strongest effects were observed in studies using morin and green tea, while Eybl et al. (2006) showed a non-significant effect. Heterogeneity was high ($I^2 = 93\%$), and funnel plot analysis revealed significant publication bias ($p < 0.001$). The increase in GSH levels indicates improved cellular antioxidant defense and redox balance. These findings are consistent with studies demonstrating that green tea and flavonoids enhance glutathione levels and antioxidant capacity (Basu et al., 2013). However, the high heterogeneity and evidence of publication bias suggest that the magnitude of effects may vary considerably depending on study conditions.

3.1.5 Antioxidant Enzyme Activity (GPx)

Six studies showed that natural antioxidants significantly increased glutathione peroxidase (GPx) activity, with a large pooled effect ($g = 2.565$, $p < 0.001$). The largest effects were observed in studies using morin and cumin, while Eybl et al. (2006) reported a non-significant effect. Heterogeneity was high ($I^2 = 87\%$), and funnel plot analysis indicated significant publication bias ($p < 0.001$). These results indicate that natural antioxidants enhance enzymatic detoxification of harmful peroxides, thereby protecting cells from oxidative damage. The findings are supported by studies showing that morin and cumin significantly improve GPx activity (Ijaz et al., 2021; Surya et al., 2005). However, variability across studies highlights the influence of methodological and biological factors on antioxidant effectiveness.

3.2 Overall Effectiveness of Natural Antioxidants

The meta-analysis demonstrated that natural antioxidants significantly reduce oxidative stress and enhance antioxidant defenses across disease models. This was evidenced by decreased MDA levels and increased SOD, CAT, GSH, and GPx activities, all showing large and statistically significant effects. Despite substantial heterogeneity ($I^2 = 85–93\%$), the overall trend consistently favored antioxidant interventions. These findings confirm the broad effectiveness of natural antioxidants in restoring redox balance and mitigating oxidative damage. The results are consistent with established literature emphasizing the role of antioxidants in reducing oxidative stress and improving cellular defense mechanisms (Higgins et al., 2020; Borenstein et al., 2022; Hedges & Vevea, 1998).

3.3 Trends in Antioxidant Efficacy Across Compounds

Polyphenols and flavonoids, including morin, curcumin, resveratrol, green tea, and quercetin, demonstrated consistently strong effects across studies. Morin and green tea showed particularly high effect sizes, while cumin and quercetin also exhibited significant antioxidant activity. Conversely, some compounds, such as apigenin and low-dose green tea, showed weaker effects. These trends suggest that the efficacy of natural antioxidants depends on their chemical composition, dosage, and bioavailability. The observed variability also reflects differences in experimental design and intervention duration, highlighting the importance of optimizing antioxidant use for therapeutic applications.

3.4 Limitations of Existing Research

The analysis revealed high heterogeneity across studies, indicating that variability in dosage, antioxidant type, and disease models influences results. Publication bias was also evident for several markers, suggesting that studies with non-significant findings may be underreported. Additionally, the reliance on animal models limits the direct applicability of results to human populations. These limitations highlight the need for more standardized methodologies and greater transparency in reporting. Differences between animal models and human conditions further emphasize the importance of validating findings through clinical research (Higgins et al., 2020; Lindsey et al., 2018; Ighodaro et al., 2017; Alaebo et al., 2025).

3.5 Future Research Directions

Future studies should focus on conducting clinical trials to validate the effectiveness of natural antioxidants in humans and determine optimal dosages. Research should also explore molecular mechanisms, synergistic effects, and long-term safety of antioxidant compounds. Advanced approaches, such as metabolomics and transcriptomics, may provide deeper insights into antioxidant action. Improving research practices through study preregistration, open data sharing, and reporting of neutral results can reduce publication bias and enhance reliability (Egger et al., 1997). These efforts will support the development of evidence-based antioxidant therapies for oxidative stress-related diseases.

4. Conclusion & Recommendations

Natural antioxidants were found to significantly reduce oxidative stress, as evidenced by decreased lipid peroxidation and increased antioxidant enzyme activities, including SOD, CAT, GSH, and GPx, across in vivo animal models. The findings consistently demonstrate that compounds such as morin, curcumin, resveratrol, green tea catechins, and quercetin enhance the body's antioxidant defense mechanisms. However, variability in study design, dosage, and treatment duration, along with potential publication bias and reliance on animal models, limits the direct applicability of these results to human clinical settings.

Future research should focus on conducting meta-analyses and clinical studies involving human participants, with standardized methodologies, comparable dosages, and clearly defined inclusion criteria. Researchers are encouraged to validate findings using multiple analytical tools and to investigate promising antioxidants such as morin, curcumin, resveratrol, green tea catechins, and quercetin in well-designed human trials. Additionally, further studies should explore molecular mechanisms and long-term effects using advanced approaches such as metabolomics and other multi-omics techniques to improve the reliability and applicability of results.

The study is limited by variability in experimental design, antioxidant dosage, and treatment duration across included studies, as well as potential publication bias that may overrepresent positive findings. Furthermore, the reliance on animal models restricts direct translation to human health due to physiological differences, and the lack of standardized protocols contributes to inconsistencies and challenges in reproducibility.

Compliance with ethical standards

This study analyzed published literature and did not involve human participants. Ethical standards were upheld through proper citation, adherence to academic integrity, and avoidance of data fabrication or falsification. Transparency and objectivity were maintained by including both positive and negative findings and conducting a comprehensive literature search. Privacy and confidentiality standards were observed, and findings were reported accurately to prevent misleading interpretations.

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