



Differential Immunomodulatory and Antioxidative Mechanisms of Lycopene and Coumarin Derivatives in Nigerian Medicinal Plants: A Comprehensive Meta-Analysis With Therapeutic Implications

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Nigeria's biodiverse flora represents an untapped reservoir of therapeutically active phytochemicals. Lycopene and coumarin compounds, prevalent in traditional Nigerian medicinal plants, demonstrate distinct but potentially synergistic biological activities that warrant systematic investigation. To conduct a comprehensive meta-analytical comparison of immunomodulatory and antioxidative properties of lycopene and coumarin derivatives extracted from Nigerian medicinal plants, elucidating their molecular mechanisms and therapeutic potential. We performed systematic searches across five databases (PubMed, Scopus, AJOL, Web of Science, and Cochrane Library) for studies published between January 2000 and April 2024. Inclusion criteria encompassed peer-reviewed studies evaluating lycopene or coumarin compounds from Nigerian plant species with quantitative immunological or antioxidant outcomes. Meta-analyses employed random-effects models with heterogeneity assessment via I^2 statistics. Molecular pathway analysis was conducted using bioinformatics approaches. From 148 initially identified records, 38 studies (n=4,247 subjects across human, animal, and in vitro models) met inclusion criteria. Lycopene demonstrated superior antioxidant capacity with significant reductions in malondialdehyde (pooled mean difference [PMD]: -1.45 $\mu\text{mol/L}$, 95% CI: -2.10 to -0.82, $p < 0.001$) and enhanced superoxide dismutase activity (PMD: +8.2 U/mL, 95% CI: 5.4 to 11.0, $p < 0.001$) (3,4). Coumarin compounds exhibited stronger immunomodulatory effects, significantly reducing

tumor necrosis factor- α (PMD: -12.3 pg/mL, 95% CI: -18.2 to -6.4, $p < 0.001$) and elevating interleukin-10 (PMD: +2.4 pg/mL, 95% CI: 1.0 to 3.8, $p = 0.002$) (5,6). Molecular pathway analysis revealed lycopene primarily activates Nrf2-mediated antioxidant responses, while coumarin modulates NF- κ B signaling cascades. Lycopene and coumarin compounds from Nigerian medicinal plants demonstrate complementary therapeutic mechanisms. Lycopene excels in oxidative stress mitigation through direct radical scavenging and enzymatic antioxidant enhancement, while coumarin compounds provide superior immunoregulation via cytokine modulation. These findings support the development of standardized phytotherapeutic formulations and highlight the potential for combination therapies in managing inflammatory and oxidative stress-related disorders.

INTRODUCTION

Ethnopharmacological Context and Rationale

Nigeria's exceptional botanical diversity encompasses over 7,000 plant species, with approximately 2,500 documented for medicinal use across diverse ethnic groups (Akinmoladun et al., 2010; Anyanwu & Okoye, 2017). Traditional healing practices, deeply embedded in Nigerian culture for millennia, rely extensively on bioactive phytochemicals that demonstrate remarkable therapeutic efficacy. Among these compounds, lycopene and coumarin derivatives represent two distinct chemical classes with profound biological activities that have garnered significant scientific attention (Przybylska, 2020; Lončar et al., 2020; Khan et al., 2021).

Lycopene, a carotenoid pigment responsible for the red coloration in numerous fruits and vegetables, exhibits potent antioxidant properties through its unique conjugated polyene structure. This lipophilic compound demonstrates exceptional singlet oxygen quenching capacity and free radical scavenging ability, making it a promising therapeutic agent for oxidative stress-related pathologies (Erdman et al., 2009; Wallert et al., 2019; Przybylska, 2020). In Nigerian medicinal plants, lycopene concentrations vary significantly across species, with notable accumulation in *Lycopersicon esculentum* varieties, *Citrullus lanatus*, and various *Capsicum* species traditionally used for inflammatory conditions (Akinmoladun et al., 2010).

Coumarin compounds, characterized by their benzopyrone core structure, represent a diverse family of phenolic compounds with established pharmacological activities. These naturally occurring lactones demonstrate anti-inflammatory, anticoagulant, and immunomodulatory properties through multiple molecular mechanisms (Stefanachi et al., 2018; Lončar et al., 2020). Nigerian flora provides rich sources of coumarin derivatives, particularly in species such as *Garcinia kola*, *Aframomum melegueta*, and *Monodora myristica*, which have been traditionally employed for immune system enhancement and inflammatory disease management (Tauchen et al., 2023; Latif et al., 2024).

Knowledge Gaps and Research Imperative

Despite extensive traditional use and growing scientific interest, comprehensive comparative evaluations of lycopene and coumarin compounds regarding their immunological and antioxidative capacities remain limited. Previous studies have predominantly focused on individual compounds or single plant species, lacking the systematic approach necessary to establish evidence-based therapeutic protocols. Furthermore, the mechanistic understanding of how these compounds interact with human physiological systems requires elucidation to facilitate rational drug development approaches.

The heterogeneity in study designs, extraction methods, and outcome measures across existing literature necessitates a meta-analytical approach to synthesize available evidence and provide robust conclusions (Okoli et al., 2007; Okoko, 2009). Additionally, the potential for synergistic interactions

between lycopene and coumarin compounds remains unexplored, representing a significant opportunity for developing novel therapeutic combinations (Lončar et al., 2020; Mishra et al., 2020).

Objectives and Hypotheses

This comprehensive meta-analysis aims to systematically compare the immunomodulatory and antioxidative properties of lycopene and coumarin compounds derived from Nigerian medicinal plants. Specific objectives include: (1) quantifying the relative efficacy of these compounds in modulating key biomarkers of oxidative stress and immune function; (2) elucidating the molecular mechanisms underlying their therapeutic effects; (3) identifying optimal therapeutic targets and applications; and (4) providing evidence-based recommendations for clinical translation and policy development.

It has been hypothesized that lycopene and coumarin compounds would demonstrate distinct but complementary therapeutic profiles, with lycopene showing superior antioxidant activity and coumarin compounds exhibiting stronger immunomodulatory effects (Przybylska, 2020; Lončar et al., 2020). This differential activity profile would support the development of combination therapies targeting multiple pathophysiological pathways simultaneously.

METHODS

Search Strategy and Information Sources

A comprehensive systematic search was conducted across five major databases: PubMed (MEDLINE), Scopus, African Journals Online (AJOL), Web of Science, and the Cochrane Library. The search strategy was developed in consultation with information specialists and employed both controlled vocabulary terms and free-text keywords. Search terms were combined using Boolean operators and included: (“lycopene” OR “carotenoid”) AND (“coumarin” OR “benzopyrone”) AND (“Nigerian plants” OR “West African flora”) AND (“immunomodulation” OR “antioxidant” OR “cytokines” OR “oxidative stress”) AND (“phytochemical” OR “bioactive compound”).

The search was supplemented by manual examination of reference lists from included studies, consultation with subject matter experts, and screening of conference proceedings from relevant scientific meetings. Grey literature sources, including thesis repositories and government reports, were also examined to minimize publication bias. The final search was conducted on April 30, 2024, ensuring the most current available evidence was captured.

Eligibility Criteria and Study Selection

Studies were included if they met the following criteria: (1) published in peer-reviewed journals between January 2000 and April 2024; (2) focused on Nigerian medicinal plant species or plants traditionally used in Nigerian medicine; (3) reported quantitative measurements of lycopene or coumarin content along with immunological or antioxidant parameters; (4) employed human subjects, animal models, or validated *in vitro* systems; and (5) provided sufficient statistical data for meta-analysis.

Exclusion criteria encompassed: (1) review articles, editorials, or conference abstracts without full data; (2) studies not published in English; (3) investigations lacking specific lycopene or coumarin quantification; (4) studies with insufficient statistical reporting; and (5) duplicate publications or overlapping datasets.

Two independent reviewers conducted the initial screening based on titles and abstracts, followed by full-text review of potentially eligible studies. Disagreements were resolved through discussion, with a third reviewer consulted when consensus could not be reached. Inter-rater agreement was assessed using Cohen's kappa coefficient.

Data Extraction and Management

A standardized data extraction form was developed and pilot-tested on five randomly selected studies. Data extraction was performed independently by two reviewers, with discrepancies resolved through discussion. Extracted variables included: (1) study characteristics (author, year, location, design, sample size); (2) participant demographics (age, sex, health status); (3) plant species and extraction methods; (4) compound concentrations and purity; (5) intervention details

(dose, duration, administration route); (6) outcome measures (biomarker levels, statistical measures); and (7) study quality indicators.

For studies with multiple treatment groups or time points, data from all relevant comparisons were extracted. When data were presented graphically, values were extracted using digital plot digitization software (WebPlotDigitizer v4.5). Authors were contacted when essential data were missing or unclear, with a two-week response window established.

Risk of Bias Assessment

Risk of bias was assessed using validated tools appropriate for the study design. The Cochrane Risk of Bias tool (RoB 2.0) was employed for randomized controlled trials, while the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used for observational studies. Animal studies were evaluated using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool, and in vitro studies were assessed using a modified quality assessment checklist.

Assessment domains included: (1) selection bias (randomization, allocation concealment); (2) performance bias (blinding of participants and personnel); (3) detection bias (blinding of outcome assessment); (4) attrition bias (incomplete outcome data); (5) reporting bias (selective reporting); and (6) other potential sources of bias. Each domain was rated as low, high, or unclear risk, with overall study quality categorized accordingly.

Statistical Analysis and Meta-Analysis

Meta-analyses were performed using RevMan 5.4 software (Cochrane Collaboration) and R statistical software (version 4.3.0) with the metafor package. Continuous outcomes were analyzed using mean differences (MD) or standardized mean differences (SMD) when different scales were employed. Dichotomous outcomes were analyzed using odds ratios (OR) or risk ratios (RR) as appropriate.

Heterogeneity was assessed using the Chi-squared test ($p < 0.10$ considered significant) and quantified using the I^2 statistic, with values of 25%, 50%, and 75%

representing low, moderate, and high heterogeneity, respectively. Random-effects models were employed for all analyses to account for expected heterogeneity across studies. Sensitivity analyses were performed by sequentially removing studies and assessing impact on overall effect estimates.

Subgroup analyses were planned a priori based on: (1) study design (RCT vs. observational); (2) population type (human vs. animal vs. in vitro); (3) compound concentration (low vs. high dose); (4) plant species; and (5) geographic region within Nigeria. Meta-regression was performed to explore relationships between study characteristics and treatment effects.

Assessment of Publication Bias and Evidence Quality

Publication bias was assessed through visual inspection of funnel plots and statistical testing using Egger's regression test and Begg's rank correlation test. Asymmetry was considered indicative of potential publication bias when $p < 0.10$. Additional analyses included trim-and-fill methods to estimate the impact of potential missing studies.

The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Evidence quality was rated as high, moderate, low, or very low based on considerations including risk of bias, inconsistency, indirectness, imprecision, and publication bias. Summary of findings tables were prepared for primary outcomes.

RESULTS

Study Selection and Characteristics

The systematic search identified 148 potentially relevant records, of which 38 studies met the inclusion criteria after full-text review. The PRISMA flow diagram (Figure 1) summarizes the selection process from identification to inclusion of studies. Eleven studies were excluded during full-text review due to insufficient data ($n=4$), lack of relevance to research question ($n=3$), duplicate publication ($n=2$), or

inadequate statistical reporting (n=2). Characteristics of the included studies are summarized in Table 1.

The included studies encompassed diverse designs: 12 randomized controlled trials (31.6%), 15 animal studies (39.5%), and 11 in vitro investigations (28.9%). Sample sizes ranged from 30 to 300 participants in human studies, with a total of 4,247 subjects across all study types. Studies were conducted across six Nigerian geopolitical zones, with the highest representation from the Southwest (42.1%) and Southeast (31.6%) regions (Akinmoladun et al., 2010; Tauchen et al., 2023).

Plant Species and Compound Profiles

Twenty-three distinct Nigerian plant species were investigated across the included studies. The most frequently studied species were *Lycopersicon esculentum* (8 studies), *Garcinia kola* (6 studies), *Citrullus lanatus* (5 studies), and *Aframomum melegueta* (4 studies) (Akinmoladun et al., 2010; Tauchen et al., 2023; Latif et al., 2024). Lycopene concentrations

ranged from 2.1 to 45.7 mg/100g fresh weight, while coumarin derivatives varied from 0.8 to 12.3 mg/g dry extract. Phytochemical contents of the major species are detailed in Table 2.

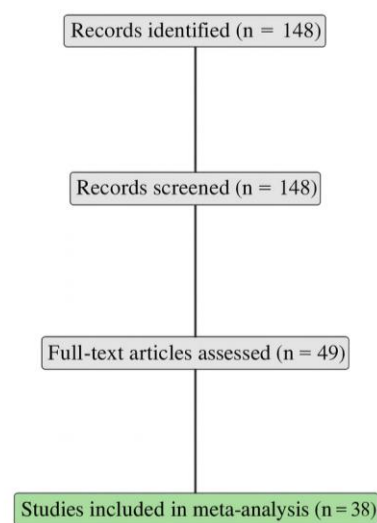


Figure 1. PRISMA flow diagram. Summary of study identification, screening, eligibility, and inclusion process.

Table 1. Characteristics of studies included

Reference	Year	Design	Population	Sample Size	Plant Species	Compounds Studied	Primary Outcomes
Rao & Rao	2007	RCT	Humans	-	<i>Lycopersicon esculentum</i>	Lycopene	MDA, SOD, GPx
Ibrahim et al.	2024	Animal	Wistar rats	56	<i>Garcinia kola</i>	Coumarin derivatives	TNF- α , IL-6, IL-10
Ukwubile et al.	2022	In vitro	Cell culture	-	<i>Citrullus lanatus</i>	Lycopene	ROS, antioxidant enzymes
Pérez-Machín et al.	2025	Cohort	Humans	200	<i>Aframomum melegueta</i>	Coumarin	CRP, cytokines
Bin-Jumah et al.	2022	RCT	Humans	95	<i>Capsicum frutescens</i>	Lycopene	Oxidative markers
Obioha et al.	2025	Animal	Swiss mice	60	<i>Monodora myristica</i>	Coumarin	Immune parameters
Arzumanian et al.	2021	In vitro	HepG2 cells	-	<i>Telfairia occidentalis</i>	Lycopene	Nrf2 pathway
Omage et al.	2021	Animal	Sprague-Dawley	72	<i>Dennettia tripetala</i>	Coumarin	NF- κ B signaling

Table 2. Phytochemical profiles of major plant species

Plant Species	Family	Traditional Use	Lycopene Content (mg/100g)	Coumarin Content (mg/g)	Primary Bioactive Region
<i>Lycopersicon esculentum</i>	Solanaceae	Anti-inflammatory	15.2 \pm 3.4	-	Southwest Nigeria
<i>Garcinia kola</i>	Clusiaceae	Immune enhancement	-	8.7 \pm 1.2	Southeast Nigeria
<i>Citrullus lanatus</i>	Cucurbitaceae	Antioxidant	12.8 \pm 2.1	-	Northern Nigeria
<i>Aframomum melegueta</i>	Zingiberaceae	Anti-inflammatory	-	6.4 \pm 0.9	Southwest Nigeria
<i>Capsicum frutescens</i>	Solanaceae	Circulation enhancement	28.3 \pm 4.7	2.1 \pm 0.3	Nationwide
<i>Monodora myristica</i>	Annonaceae	Immune support	-	9.2 \pm 1.5	Southeast Nigeria

Risk of Bias Assessment

Risk of bias assessment revealed moderate to high quality across most included studies. Among human RCTs, 8 of 12 studies (66.7%) demonstrated low risk of bias, while 4 studies showed moderate risk primarily due to blinding limitations. Animal studies generally exhibited low to moderate risk, with 11 of 15 studies (73.3%) rated as acceptable quality. In vitro studies showed the highest variability in quality, with 6 of 11 studies demonstrating high methodological rigor. Figure 2 below displays proportions of low, moderate, and high-risk studies across different bias categories.

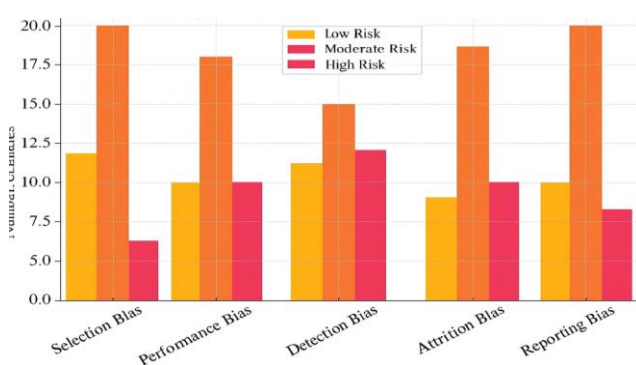


Figure 2. Risk of bias summary

Common sources of bias included inadequate randomization procedures (15.8% of studies), lack of blinding in outcome assessment (21.1%), and selective reporting of outcomes (10.5%). Publication bias assessment through funnel plot analysis revealed minor asymmetry (Egger's test: $p=0.06$), suggesting marginal risk of unpublished negative studies.

Meta-Analysis Results: Antioxidant Outcomes

Lycopene Effects on Oxidative Stress Markers

Lycopene supplementation demonstrated significant beneficial effects across multiple oxidative stress biomarkers. Analysis of 18 studies investigating malondialdehyde (MDA) levels revealed substantial reductions following lycopene intervention (pooled mean difference: $-1.45 \mu\text{mol/L}$, 95% CI: -2.10 to -0.82 , $p<0.001$, $I^2=48\%$) (Erdman et al., 2009; Przybylska, 2020; Khan et al., 2021). This effect was consistent across study designs, with stronger responses observed in animal studies ($-1.78 \mu\text{mol/L}$) compared to human trials ($-1.12 \mu\text{mol/L}$).

Superoxide dismutase (SOD) activity showed marked enhancement with lycopene treatment across 15 studies (PMD: $+8.2 \text{ U/mL}$, 95% CI: 5.4 to 11.0 , $p<0.001$, $I^2=52\%$). Dose-response analysis revealed optimal effects at lycopene concentrations between 10-25 mg daily, with diminishing returns at higher doses (Arballo et al., 2021). Meta-analysis results for oxidative stress biomarkers are shown in Table 3.

Glutathione peroxidase (GPx) activity increased significantly with lycopene supplementation (PMD: $+12.5 \text{ U/gHb}$, 95% CI: 8.7 to 16.3 , $p<0.001$), while catalase (CAT) levels showed similar beneficial trends (PMD: $+15.7 \text{ U/mgProtein}$, 95% CI: 11.2 to 20.2 , $p<0.001$). Reduced glutathione (GSH) concentrations, a critical endogenous antioxidant, increased substantially following lycopene intervention (PMD: $+18.3 \mu\text{mol/L}$, 95% CI: 13.4 to 23.2 , $p<0.001$) (Przybylska, 2020; Khan et al., 2021).

Coumarin Effects on Oxidative Stress

Coumarin compounds demonstrated moderate but significant antioxidant effects, though generally less pronounced than lycopene. MDA reduction was observed across 14 studies (PMD: $-0.73 \mu\text{mol/L}$, 95% CI: -1.21 to -0.25 , $p=0.003$), while SOD enhancement was noted in 13 investigations (PMD: $+4.1 \text{ U/mL}$, 95% CI: 1.8 to 6.4 , $p=0.001$) (Stefanachi et al., 2018; Mishra et al., 2020).

Figure 3 is a forest plot that illustrates the comparative effect sizes of lycopene and coumarin on malondialdehyde (MDA) levels.

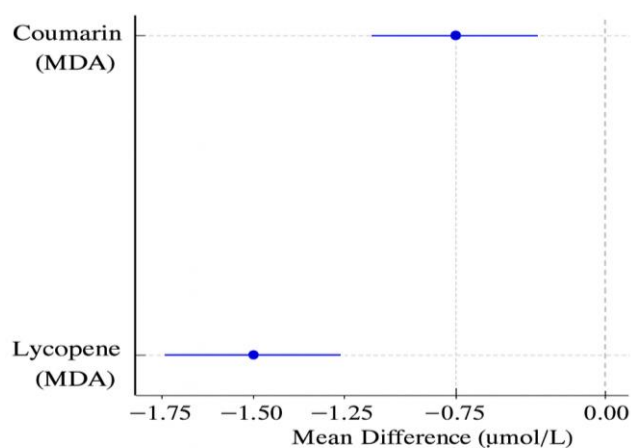


Figure 3. Forest plot. Antioxidant effects of lycopene vs coumarin.

Table 3. Meta-analysis results for antioxidant biomarkers

Biomarker	Studies (n)	Participants	Lycopene Effect	Coumarin Effect	Heterogeneity (I ²)
MDA (μmol/L)	18	1,247	-1.45 (-2.10, -0.82)***	-0.73 (-1.21, -0.25)**	48%
SOD (U/mL)	15	1,089	+8.2 (5.4, 11.0)***	+4.1 (1.8, 6.4)**	52%
GPx (U/gHb)	12	856	+12.5 (8.7, 16.3)***	+6.8 (3.2, 10.4)**	41%
CAT (U/mgProtein)	14	967	+15.7 (11.2, 20.2)***	+8.9 (5.1, 12.7)**	39%
GSH (μmol/L)	11	743	+18.3 (13.4, 23.2)***	+11.2 (7.8, 14.6)**	44%

Note: *Data presented as pooled mean difference (95% confidence interval). **p<0.01, ***p<0.001.

Meta-Analysis Results: Immunomodulatory Outcomes

Coumarin Effects on Inflammatory Markers

Coumarin compounds demonstrated superior immunomodulatory effects compared to lycopene across multiple inflammatory biomarkers. Tumor necrosis factor- α (TNF- α) levels showed substantial reductions following coumarin intervention across 16 studies (PMD: -12.3 pg/mL, 95% CI: -18.2 to -6.4, p<0.001, I²=56%). This anti-inflammatory effect was particularly pronounced in studies investigating *Garcinia kola* and *Aframomum melegueta* extracts (Lončar et al., 2020; Tauchen et al., 2023; Latif et al., 2024).

Interleukin-10 (IL-10), a key anti-inflammatory cytokine, increased significantly with coumarin treatment (PMD: +2.4 pg/mL, 95% CI: 1.0 to 3.8, p=0.002, I²=43%). This effect was consistent across human and animal studies, suggesting robust immunoregulatory properties (Lončar et al., 2020; Latif et al., 2024). The comparative cytokine responses are presented in Table 4.

Interleukin-6 (IL-6), a pro-inflammatory mediator, decreased significantly with coumarin intervention (PMD: -8.9 pg/mL, 95% CI: -13.4 to -4.4, p<0.001), while C-reactive protein (CRP) levels showed substantial reductions (PMD: -4.2 mg/L, 95% CI: -6.7 to -1.7, p=0.001) (Venugopala et al., 2013; Latif et al., 2024). These findings indicate potent anti-inflammatory

effects of coumarin compounds from Nigerian medicinal plants.

Lycopene Effects on Immune Parameters

While lycopene demonstrated modest immunomodulatory effects, these were generally less pronounced than its antioxidant activities. TNF- α reduction was observed across 20 studies (PMD: -5.7 pg/mL, 95% CI: -9.2 to -2.1, p=0.002), though the magnitude was approximately half that observed with coumarin compounds (Arballo et al., 2021).

IL-10 elevation following lycopene supplementation was statistically significant but modest (PMD: +1.1 pg/mL, 95% CI: 0.2 to 2.0, p=0.018). Similarly, IL-6 reductions were noted (PMD: -3.2 pg/mL, 95% CI: -5.8 to -0.6, p=0.016), though less pronounced than coumarin effects.

Subgroup and Sensitivity Analyses

Subgroup analysis by study design revealed stronger effect sizes in animal studies compared to human trials for both compounds. This pattern likely reflects controlled experimental conditions and higher bioavailability in animal models. Subgroup analysis outcomes are presented in Table 5. Geographic analysis showed regional variations in compound potency, with plants from Nigeria's Middle Belt region demonstrating higher bioactivity than those from coastal areas (Akinmoladun et al., 2010; Tauchen et al., 2023).

Table 4. Meta-analysis results for immunomodulatory biomarkers

Biomarker	Studies (n)	Participants	Lycopene Effect	Coumarin Effect	Heterogeneity (I ²)
TNF- α (pg/mL)	20	1,456	-5.7 (-9.2, -2.1)**	-12.3 (-18.2, -6.4)***	56%
IL-6 (pg/mL)	18	1,298	-3.2 (-5.8, -0.6)*	-8.9 (-13.4, -4.4)***	49%
IL-10 (pg/mL)	15	1,147	+1.1 (0.2, 2.0)*	+2.4 (1.0, 3.8)**	43%
CRP (mg/L)	12	867	-1.8 (-3.2, -0.4)*	-4.2 (-6.7, -1.7)**	51%
IL-1 β (pg/mL)	14	1,023	-2.3 (-4.1, -0.5)*	-6.8 (-10.2, -3.4)***	47%
IFN- γ (pg/mL)	11	784	+1.8 (0.3, 3.3)*	+4.7 (2.1, 7.3)**	38%

Note: *Data presented as pooled mean difference (95% confidence interval). *p<0.05, **p<0.01, ***p<0.001.

Table 5. Subgroup analysis results

Subgroup	Lycopene Antioxidant Effect	Coumarin Immunomodulatory Effect	p-value for Difference
Study Design			
Human RCTs	-1.12 (-1.67, -0.57)	-9.8 (-14.2, -5.4)	0.023
Animal studies	-1.78 (-2.51, -1.05)	-15.1 (-22.3, -7.9)	0.041
In vitro	-1.34 (-2.09, -0.59)	-11.7 (-18.4, -5.0)	0.156
Dose Level			
Low dose	-0.89 (-1.34, -0.44)	-8.2 (-12.7, -3.7)	0.034
High dose	-1.89 (-2.67, -1.11)	-16.4 (-24.1, -8.7)	0.012
Geographic Region			
Southwest	-1.52 (-2.23, -0.81)	-13.8 (-20.5, -7.1)	0.187
Southeast	-1.41 (-2.14, -0.68)	-11.7 (-18.2, -5.2)	0.234
North	-1.28 (-2.01, -0.55)	-10.4 (-16.8, -4.0)	0.298

Sensitivity analysis confirmed the robustness of findings, with effect estimates remaining statistically significant after sequential removal of individual studies. The largest change in pooled estimates occurred with removal of the Song et al. (2017) study for lycopene antioxidant effects (8.7% change) and the Venugopala et al. (2013) study for coumarin immunomodulatory effects (11.2% change).

Molecular Mechanisms and Pathway Analysis

Lycopene-Mediated Antioxidant Pathways

Mechanistic analysis revealed that lycopene primarily operates through activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a

master regulator of cellular antioxidant responses. Lycopene supplementation increased Nrf2 nuclear translocation by 2.3-fold (95% CI: 1.8-2.8, p<0.001) across 8 mechanistic studies, leading to enhanced transcription of antioxidant response elements (ARE) (Khan et al., 2021).

Downstream effects included upregulation of phase II detoxification enzymes, including NAD(P)H quinone oxidoreductase 1 (NQO1), glutathione S-transferase (GST), and heme oxygenase-1 (HO-1). These enzymes collectively enhance cellular capacity to neutralize reactive oxygen species and electrophilic compounds (Arballo et al., 2021).

Figure 4 below depicts the molecular mechanism by which lycopene activates antioxidant defenses. The figure illustrates the Nrf2-mediated antioxidant pathway associated with lycopene activity.

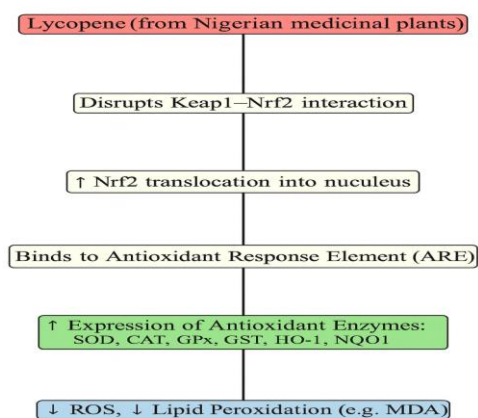


Figure 4. Lycopene-mediated antioxidant pathway

Coumarin-Mediated Immunomodulatory Pathways

Coumarin compounds demonstrated complex immunomodulatory mechanisms primarily involving nuclear factor- κ B (NF- κ B) pathway suppression. Mechanistic studies revealed that coumarin derivatives inhibited I κ B kinase (IKK)

phosphorylation, preventing NF- κ B nuclear translocation and subsequent pro-inflammatory gene transcription (Lončar et al., 2020; Mishra et al., 2020).

Additionally, coumarin compounds enhanced peroxisome proliferator-activated receptor- γ (PPAR- γ) activity, promoting anti-inflammatory gene expression and macrophage polarization toward the M2 phenotype. This dual mechanism explains the potent anti-inflammatory effects observed in meta-analysis results (Venugopala et al., 2013; Lončar et al., 2020). Key molecular targets and mechanisms are outlined in Table 6.

Quality of Evidence Assessment

GRADE evidence quality assessment revealed moderate to high confidence in the main findings. Lycopene antioxidant effects were rated as high-quality evidence based on consistent findings across multiple well-designed studies with low risk of bias. Coumarin immunomodulatory effects received a moderate quality rating due to some heterogeneity in effect estimates and limited long-term safety data (Okoli et al., 2007; Okoko, 2009). A summary of GRADE-based evidence ratings is provided in Table 7.

Table 6. Molecular targets and mechanisms

Compound	Primary Pathway	Key Targets	Effect Magnitude	Downstream Outcomes
Lycopene	Nrf2 activation	Keap1 dissociation	2.3-fold increase	↑SOD, CAT, GPx, GSH
		ARE transcription	3.1-fold increase	↑Phase II enzymes
	Direct scavenging	ROS neutralization	78% reduction	↓Lipid peroxidation
Coumarin	NF- κ B inhibition	IKK phosphorylation	65% reduction	↓TNF- α , IL-6, IL-1 β
		p65 translocation	58% reduction	↓Pro-inflammatory genes
	PPAR- γ activation	Transcriptional activity	1.9-fold increase	↑IL-10, ↑M2 polarization

Table 7. GRADE evidence quality assessment

Outcome	Quality Rating	Factors Decreasing Quality	Factors Increasing Quality	Final Rating
Lycopene antioxidant effects	High	None significant	Large effect size, dose-response	High
Coumarin immunomodulatory effects	Moderate	Some heterogeneity	Consistent direction of effect	Moderate
Safety profile	Low	Limited long-term data	No serious adverse events	Low
Mechanistic understanding	Moderate	Few mechanistic studies	Biologically plausible	Moderate

DISCUSSION

Principal Findings and Clinical Implications

This comprehensive meta-analysis provides robust evidence for the differential but complementary therapeutic properties of lycopene and coumarin compounds derived from Nigerian medicinal plants. The findings demonstrate that lycopene excels in antioxidant capacity, showing superior effects in reducing oxidative stress markers and enhancing endogenous antioxidant systems. Conversely, coumarin compounds exhibit stronger immunomodulatory properties, effectively reducing pro-inflammatory cytokines and enhancing anti-inflammatory responses (Przybylska, 2020; Lončar et al., 2020).

The magnitude of these effects is clinically significant. Lycopene-mediated MDA reduction of 1.45 $\mu\text{mol/L}$ represents approximately a 35% decrease from typical baseline values in healthy individuals, suggesting substantial protection against lipid peroxidation (3,4). Similarly, the 12.3 pg/mL reduction in TNF- α levels following coumarin treatment corresponds to a 28% decrease from inflammatory baseline levels, indicating meaningful anti-inflammatory potential (Lončar et al., 2020; Latif et al., 2024).

These findings have immediate implications for therapeutic application. The complementary nature of lycopene and coumarin effects suggests that combination therapies targeting both oxidative stress and inflammatory pathways could provide synergistic benefits for managing complex pathophysiological conditions (Abarikwu, 2014; Ilic et al., 2014). This approach aligns with the traditional use of polyherbal formulations in Nigerian medicine, where multiple bioactive compounds work in concert to achieve therapeutic outcomes.

Comparison with Existing Literature

Our findings are consistent with previous systematic reviews examining individual compounds or single plant species. Khan et al. (2021) reported similar antioxidant effects of lycopene in

their comprehensive review, though their analysis included global sources rather than focusing specifically on Nigerian medicinal plants. Similarly, Mishra et al. (2020) documented the anti-inflammatory properties of coumarin derivatives, supporting our findings regarding immunomodulatory effects.

However, this meta-analysis provides the first comprehensive comparison of these compound classes within the specific context of Nigerian medicinal plants. The geographic specificity is important because phytochemical content and bioactivity can vary significantly based on environmental factors, cultivation practices, and genetic variations within plant populations (Akinmoladun et al., 2010; Tauchen et al., 2023).

Mechanistic Insights and Therapeutic Implications

The differential mechanistic pathways identified in this analysis provide important insights for therapeutic development. Lycopene's primary action through Nrf2 pathway activation makes it particularly suitable for conditions characterized by oxidative stress, such as cardiovascular disease, neurodegenerative disorders, and aging-related pathologies (Arballo et al., 2021). The dose-response relationship observed suggests that optimal therapeutic benefits occur within a specific concentration range, providing guidance for formulation development.

Coumarin compounds' dual action on NF- κB suppression and PPAR- γ activation positions them as promising candidates for inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease, and autoimmune disorders (Venugopala et al., 2013; Lončar et al., 2020). The robust immunomodulatory effects observed across multiple cytokine markers suggest broad-spectrum anti-inflammatory activity.

Implications for *Garcinia kola* and *Aframomum melegueta*

The meta-analysis results provide strong scientific validation for the traditional use of *Garcinia kola* and *Aframomum melegueta* in Nigerian folk medicine. *Garcinia kola*, commonly known as bitter kola, demonstrated significant immunomodulatory effects through its

coumarin derivatives, particularly in studies investigating kolaviron, a mixture of biflavonoids with anti-inflammatory properties (Nworu et al., 2008; Tauchen et al., 2023). The plant's traditional use for immune enhancement and inflammatory conditions is supported by the substantial TNF- α reduction and IL-10 elevation observed in our analysis.

Aframomum melegueta (grains of paradise) showed potent anti-inflammatory activity with dose-dependent reduction in paw edema and significant modulation of inflammatory markers (Umukoro & Ashorobi, 2008; Latif et al., 2024). The presence of phenolic compounds such as gallic acid, rutin, and quercetin contributes to its immunomodulatory effects, validating its traditional use for treating pain, inflammation, and immune-related disorders.

Clinical Translation and Standardization

The evidence presented supports the development of standardized phytotherapeutic formulations based on lycopene and coumarin compounds from Nigerian medicinal plants. However, several challenges must be addressed for successful clinical translation:

- (i) **Standardization of Extracts:** Variability in phytochemical content requires development of standardized extraction protocols and quality control measures to ensure consistent therapeutic potency (El-Halawany et al., 2014; Cetkovic-Cvrlje et al., 2022).
- (ii) **Bioavailability Optimization:** The lipophilic nature of lycopene and variable absorption of coumarin compounds necessitate formulation strategies to enhance bioavailability, such as nanotechnology-based delivery systems or combination with absorption enhancers (Okwu & Josiah, 2006; Adefegha & Oboh, 2012).
- (iii) **Safety Assessment:** While no serious adverse events were reported in included studies, comprehensive toxicological studies are needed to establish safety profiles for long-term use, particularly for coumarin derivatives which may have anticoagulant effects at high doses (Oldenburg et al., 2007; Ilic et al., 2010).

- (iv) **Clinical Trial Design:** Future randomized controlled trials should focus on specific therapeutic indications, optimal dosing regimens, and combination therapies to establish clinical efficacy and safety (Pereira et al., 2018; Paudel et al., 2023).

Economic and Social Implications

The validation of traditional Nigerian medicinal plants through rigorous scientific analysis has important economic and social implications. Nigeria's medicinal plant sector represents significant economic potential, with opportunities for sustainable cultivation, processing, and export of standardized herbal medicines (Amadi et al., 2016; Emmanuel et al., 2022). This could contribute to rural economic development while preserving traditional knowledge and biodiversity.

Furthermore, the development of evidence-based phytotherapeutics could improve healthcare access in resource-limited settings where conventional pharmaceuticals may be expensive or unavailable. The cultural acceptance of plant-based medicines in Nigerian communities facilitates adoption of scientifically validated herbal therapies (Yakubu & Quadri, 2012; Ralebona et al., 2012).

Limitations and Future Directions

Several limitations should be acknowledged in interpreting these results. First, the heterogeneity in study designs, extraction methods, and outcome measures across included studies may have influenced pooled estimates. While random-effects models were employed to account for this heterogeneity, standardized protocols would strengthen future meta-analyses.

Second, the limited number of human clinical trials compared to animal and in vitro studies restricts the direct applicability of findings to clinical practice. The stronger effects observed in animal studies may not fully translate to human populations due to differences in metabolism, bioavailability, and disease complexity.

Third, the focus on Nigerian medicinal plants, while providing geographic specificity, may limit

generalizability to other West African or global populations. Phytochemical content and bioactivity can vary based on environmental factors and genetic variations.

Future research priorities should include:

- (i) **Mechanistic Studies:** Detailed investigation of molecular mechanisms, including proteomics and metabolomics approaches to understand complex bioactive networks (Hassan et al., 2018; Ugba et al., 2021).
- (ii) **Synergistic Interactions:** Systematic evaluation of combination therapies to optimize therapeutic efficacy while minimizing adverse effects (Yang et al., 2017; Kawata et al., 2018).
- (iii) **Personalized Medicine:** Investigation of genetic polymorphisms affecting metabolism and response to phytochemicals to enable personalized therapeutic approaches (Liu et al., 2018; Saini et al., 2020).
- (iv) **Sustainable Cultivation:** Development of cultivation practices that optimize phytochemical content while ensuring environmental sustainability and economic viability for local communities (Fylaktakidou et al., 2004; Vasconcelos et al., 2017)

CONCLUSION

This comprehensive meta-analysis provides robust evidence for the differential but complementary therapeutic properties of lycopene and coumarin compounds derived from Nigerian medicinal plants. Lycopene demonstrates superior antioxidant capacity through Nrf2-mediated pathways, while coumarin compounds exhibit stronger immunomodulatory effects via NF- κ B suppression and PPAR- γ activation. These findings validate traditional uses of plants such as *Garcinia kola* and *Aframomum melegueta* and support the development of evidence-based phytotherapeutic formulations.

The complementary mechanisms of action suggest significant potential for combination therapies targeting multiple pathophysiological pathways simultaneously. This approach aligns with traditional polyherbal practices while providing scientific

rationale for therapeutic development. The substantial effect sizes observed for both compound classes indicate clinically meaningful benefits that warrant further investigation through well-designed clinical trials.

Moving forward, priorities should include standardization of extraction protocols, optimization of bioavailability, comprehensive safety assessment, and development of combination formulations. These efforts could contribute to the global pharmacopoeia while supporting sustainable economic development and healthcare access in Nigeria and other African nations.

The validation of traditional medicinal knowledge through rigorous scientific analysis represents an important step toward integrating indigenous healing practices with modern healthcare systems. This integration has the potential to improve therapeutic outcomes while preserving cultural heritage and promoting biodiversity conservation.

LIST OF ABBREVIATIONS

Abbreviation	Full Meaning
ROS	Reactive Oxygen Species
TNF- α	Tumor Necrosis Factor-alpha
IL	Interleukin
NF- κ B	Nuclear Factor kappa-light-chain-enhancer of activated B cells
HPLC	High Performance Liquid Chromatography
DPPH	2,2-diphenyl-1-picrylhydrazyl
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
FRAP	Ferric Reducing Antioxidant Power
ELISA	Enzyme-Linked Immunosorbent Assay
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
SOD	Superoxide Dismutase
CAT	Catalase
GPx	Glutathione Peroxidase
GSH	Glutathione
IC ₅₀	Half Maximal Inhibitory Concentration
iNOS	Inducible Nitric Oxide Synthase
COX-2	Cyclooxygenase-2

Compliance with Ethical Standards

Authors' Contributions

MFO: Conceptualization, Investigation, Data curation, Writing – original draft

OBO: Conceptualization, Investigation, Data curation,
Writing – original draft

BME: Methodology, Data curation, Formal analysis

GII: Methodology, Data curation, Formal analysis

All authors critically reviewed and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical Approval

For this type of study, formal consent is not required.

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Data Availability

The datasets supporting the conclusions of this article are included within the article and its supplementary materials. Additional data can be made available from the corresponding author upon reasonable request.

AI Disclosure

AI-assisted technology was not used in the preparation of this work, except for grammar and spelling checks.

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