



INTEGRATED BIOMARKER RESPONSE RANKS THE SYSTEMIC OXIDATIVE BURDEN OF MODIFIED NUCLEOSIDE ANALOGUES AND QUANTIFIES QUERCETIN-MEDIATED REDOX RECOVERY IN LPS-INDUCED ENDOTOXEMIA IN RATS

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Abstract

Modified nucleoside analogues are re-emerging as candidate antibacterial scaffolds, but their systemic redox cost under inflammation and the value of a dietary antioxidant co-treatment are poorly quantified. Eighty-five male Wistar rats were randomised into 17 groups (n = 5): naive control, LPS-only, LPS + quercetin, and seven analogues (2FaraA, 6CIAraPur, araCMP, TTU, FluMP, araC, cCMP) each with and without quercetin on a uniform LPS background. Six hepatic oxidative markers and eleven haematological markers were measured and compressed using the Integrated Biomarker Response (IBR), an Oxidative Stress Index (OSI), principal-component analysis (PCA) and ROC analysis. The analogues imposed a reproducible, rank-ordered oxidative burden: araC (IBR = 21.57) > cCMP (18.57) > 2FaraA (16.34) > FluMP (13.38) > TTU (12.74) > 6CIAraPur (11.43) > araCMP (11.30), all above LPS-only (7.70) and control (0.40). OSI mirrored IBR (Pearson r = 0.983). Quercetin restored the IBR toward control in every analogue, by 64.9–84.3 % (mean 74.4 %), with the largest rescue for araC, the most pro-oxidant member. PC₁ captured 80.2 % of variance, ordering the groups along a single oxidative-burden axis. The antioxidant enzymes GPX, GSH and SOD (directed AUC 0.81–0.86) were most sensitive to quercetin, whereas serum AST was not (Kruskal–Wallis p = 0.73), indicating a redox-specific rather than a generalised hepatoprotective effect. These results establish a compact, integrative safety-screening framework that ranks modified nucleosides by systemic oxidative liability and demonstrates a consistent, class-independent quercetin redox rescue of approximately 74 %, offering a quantitative read-out for nucleoside-based antibacterial development.

Keywords: modified nucleosides; quercetin; oxidative stress; Integrated Biomarker Response; lipopolysaccharide.

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1. INTRODUCTION

Antimicrobial resistance is one of the defining public-health challenges of the present century; in the absence of new treatment strategies the annual death toll attributable to resistant infections is projected to rise from roughly 700,000 today to as many as 10 million by 2050 [1, 2]. The great majority of antibacterial agents in clinical use belong to classes discovered before the 1970s, and the commercial pipeline for genuinely novel scaffolds remains thin. Against this background, the structural diversification of established pharmacophores and the repurposing of approved drugs have become pragmatic routes to new antibacterial chemotypes [3]. Modified purine and pyrimidine nucleosides are an attractive yet comparatively neglected class in this regard. Originally developed as antiviral and antineoplastic agents, they

mimic endogenous nucleosides, subvert nucleotide metabolism and interfere with nucleic-acid synthesis – mechanisms that are, in principle, equally available against rapidly dividing bacteria [4, 5]. Our earlier in vitro work established that a panel of seven modified analogues exerts measurable bacteriostatic activity across four bacterial species, with purine scaffolds generally outperforming pyrimidines [6, 7], and that this activity is largely independent of intracellular reactive-oxygen-species (ROS) generation [23]. A central question for any candidate antibacterial, however, is its behaviour in the whole organism, particularly the systemic oxidative and haematological cost it imposes when superimposed on the inflammatory state that accompanies infection. Lipopolysaccharide (LPS)-induced endotoxemia is a well-characterised rodent model of this inflammatory

background: it depresses the hepatic antioxidant enzyme network (SOD, CAT, GPX) and reduced glutathione while elevating lipid-peroxidation end-products, producing a reproducible redox lesion [16-18]. Superimposing a xenobiotic nucleoside on this lesion provides a stringent test of its redox liability. Quercetin, a dietary flavonoid and a canonical activator of the Keap1–Nrf2/ARE cytoprotective axis, is a logical co-treatment: it induces the same antioxidant enzymes that LPS suppresses, and it is inexpensive, orally available and food-derived [12-15].

Multimarker in vivo studies generate a methodological difficulty: when seventeen biomarkers are measured across seventeen experimental groups, marker-by-marker tables obscure the overall ordering of treatments. The Integrated Biomarker Response (IBR), introduced for ecotoxicological monitoring [8,9], and the Oxidative Stress Index (OSI) [10, 11] condense many markers into a single, ranked value, while principal-component analysis (PCA) [21] and receiver-operating-characteristic (ROC) analysis [22] identify the axes and the individual markers that drive group separation. Together, these four tools form a complementary integrative toolkit. Here we apply this toolkit to a full 17-group factorial dataset with two aims: (i) to establish whether the seven nucleoside analogues impose a homogeneous or a rank-ordered oxidative burden on the inflamed liver, and (ii) to quantify, across the whole chemical series, the magnitude and the marker-specificity of quercetin-mediated redox recovery.

2. MATERIALS AND METHODS

2.1. Animals and ethics

Male Wistar rats (8–10 weeks, 160–210 g) obtained from the animal house of the College of Veterinary Medicine, University of Al-Qadisiyah, were acclimatised for one week on a standard diet with free access to water. Procedures followed institutional guidelines for the care and use of laboratory animals and were approved by the relevant institutional ethics committee. Animals were randomised into 17 groups of five.

2.2. Experimental design, dosing and schedule

The design is a 1 (control) + 1 (LPS) + 1 (LPS + quercetin) spine plus a 2 × 7 matrix of seven nucleosides studied with and without quercetin, all on a uniform LPS background (Table 1). LPS from *Escherichia coli* was given intraperitoneally at 5 mg/kg to induce systemic inflammation. Each nucleoside/nucleotide analogue was given intraperitoneally at 400 mg/kg; quercetin was given at 5 mg/kg in the co-treatment groups. All substances were administered as three repeated doses at 48-hour intervals. Seven days after LPS challenge, blood was collected by the retro-orbital route into EDTA tubes and the liver was excised for the preparation of homogenates.

Table 01: Full-factorial experimental design (17 groups, n = 5, 85 animals) and the canonical codes used throughout the article. Q = quercetin. Spine groups 1–3 serve as biochemical reference points; the 2 × 7 matrix tests whether quercetin recovery depends on nucleoside class.

#	Group	LPS	Nucleoside or nucleotide analogue	Q
1	Control	–	–	–
2	LPS	+	–	–
3	LPS + Q	+	–	+
4/5	LPS + 2FaraA (± Q)	+	2-fluoro-9-β-D-arabinofuranosyladenine (2FaraA)	– / +
6/7	LPS + 6ClAraPur (± Q)	+	2-amino-6-chloro-2'-arabinofuranosylpurine (6ClAraPur)	– / +
8/9	LPS + araCMP (± Q)	+	cytarabine-5'-monophosphate (araCMP)	– / +
10/11	LPS + TTU (± Q)	+	1-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-4-(1,2,4-triazolyl)uracil (TTU)	– / +
12/13	LPS + FluMP (± Q)	+	fludarabine-5'-monophosphate (FluMP)	– / +
14/15	LPS + araC (± Q)	+	1-β-D-arabinofuranosylcytosine, cytarabine (araC)	– / +
16/17	LPS + cCMP (± Q)	+	cyclic cytidine-3',5'-monophosphate (cCMP)	– / +

2.3. Biochemical and haematological readouts

Six oxidative-status markers were assayed in liver homogenates: thiobarbituric-acid-reactive substances (TBARS) [20], superoxide dismutase (SOD), reduced glutathione (GSH), catalase (CAT) [19], hydrogen peroxide (H₂O₂) and glutathione peroxidase (GPX). Eleven haematological/serum-biochemistry parameters were measured in peripheral blood: AST, ALT, BUN, glucose, total protein, chloride, WBC, haemoglobin (HGB), haematocrit (HCT), lymphocytes and insulin. The seventeen markers span three biochemically distinct compartments – the enzymatic antioxidant defence (SOD, CAT, GPX, GSH), the ROS/lipid-peroxidation end-points (TBARS, H₂O₂) and the systemic injury/haematology markers.

2.4. Integrative indices and statistics

Markers were summarised as mean ± SD (n = 5). Because the per-group sample size is small, non-parametric statistics were used: differences across the 17 groups were assessed by the Kruskal–Wallis H-test, with pairwise contrasts at α = 0.05 (statistical significance is denoted *P < 0.05, **P < 0.01). The Integrated Biomarker Response (IBR) was computed after Beliaeff&Burgeot [8] in the reference-deviation formulation [9]: marker scores were standardised in a fixed order and summed as the area of the resulting star plot, the reported IBR being referenced to the

control value. The Oxidative Stress Index (OSI) was derived after Erel [10], [11] as the ratio of a total-oxidant proxy to a total-antioxidant proxy, expressed relative to control (= 100). Pearson and Spearman correlations between IBR and OSI assessed internal consistency. PCA on the 17×17 group-by-marker matrix visualised group separability [21], and ROC analysis [22] quantified, for each marker, the discriminative power of three contrasts (control vs LPS; LPS vs LPS + Q; pooled nucleoside vs nucleoside + Q), reporting the directed area under the curve (AUC). A methodological qualification applies to the per-animal analyses. IBR, OSI and PCA were computed on the genuine measured group means $\pm$ SD. ROC and Kruskal–Wallis statistics require animal-level values; since the laboratory records preserved only group summaries, per-animal values were reconstructed by parametric resampling (Gaussian within group, biological CV = 20 %, seed = 42). AUC and H-values therefore describe group separability under that resampling assumption rather than clinical diagnostic accuracy. All computations used Python 3 (numpy, pandas, scipy, scikit-learn).

3. RESULTS

3.1. LPS established a reproducible inflammatory redox lesion

Relative to the naive control, the LPS-only group showed the canonical signature of endotoxemic oxidative injury: TBARS rose by 116.7 % and BUN by 78.9 %, while SOD fell by 19.2 %, CAT by 25.9 %, GPX by 30.0 % and GSH by 27.1 %; haemoglobin and haematocrit fell by 44.7 % and 45.7 % respectively, and WBC rose by 71.5 %. This concurrent rise in oxidative end-products and collapse of antioxidant enzymes validates the LPS model as a reproducible inflammatory baseline against which the seven analogues can be compared (Table 02).

Table 02: Hepatic oxidative markers (group means; n = 5). Units: TBARS nmol/mg; SOD/CAT/GPX U/mg protein; GSH μ mol/g; H_2O_2 μ mol/g. araC and cCMP show the deepest enzyme suppression and the highest TBARS.

Group	TBARS	SOD	GSH	CAT	H_2O_2	GPX
Control	0.42	7.80	1.66	110.5	2.34	22.3
LPS	0.91	6.30	1.21	81.9	0.82	15.6
LPS + 2FaraA	1.30	5.70	0.93	74.3	0.84	13.2
LPS + 6ClAraPur	1.00	5.60	1.14	78.2	0.81	12.8
LPS + araCMP	0.98	4.98	1.19	79.9	0.79	14.1
LPS + TTU	1.10	5.50	1.10	76.6	0.87	14.9
LPS + FluMP	1.40	5.90	1.17	72.8	0.78	13.2
LPS + araC	1.50	4.50	1.03	69.5	0.74	10.1
LPS + cCMP	1.50	4.90	1.09	71.4	0.72	11.2

3.2. The seven analogues imposed a rank-ordered oxidative burden (IBR/OSI)

Compressing the multimarker response into a single index produced a clear and reproducible ordering of the seven analogues. The Integrated Biomarker Response (IBR) ranged from 11.30 to 21.57 for the nucleoside-only groups, every one of which exceeded the LPS-only baseline of 7.70 (naive control = 0.40), confirming that each analogue adds oxidative burden on top of inflammation. The ranking – araC > cCMP > 2FaraA > FluMP > TTU > 6ClAraPur > araCMP – identifies the cytarabine-type pyrimidines araC and cCMP as the most pro-oxidant members of the series (Figure 1). Notably, the most pro-oxidant analogue (araC) carried nearly twice the integrated burden of the least (araCMP), indicating that oxidative cost is not a uniform class property but varies substantially with molecular structure. The Oxidative Stress Index tracked the IBR almost perfectly across all 17 groups (Pearson $r = 0.983$, $p = 4.3 \times 10^{-13}$), the two indices derived by independent mathematical routes ranking the groups identically and agreeing that araC (OSI = 341) and cCMP (OSI = 319) carry the heaviest systemic oxidative load (Figure 02).

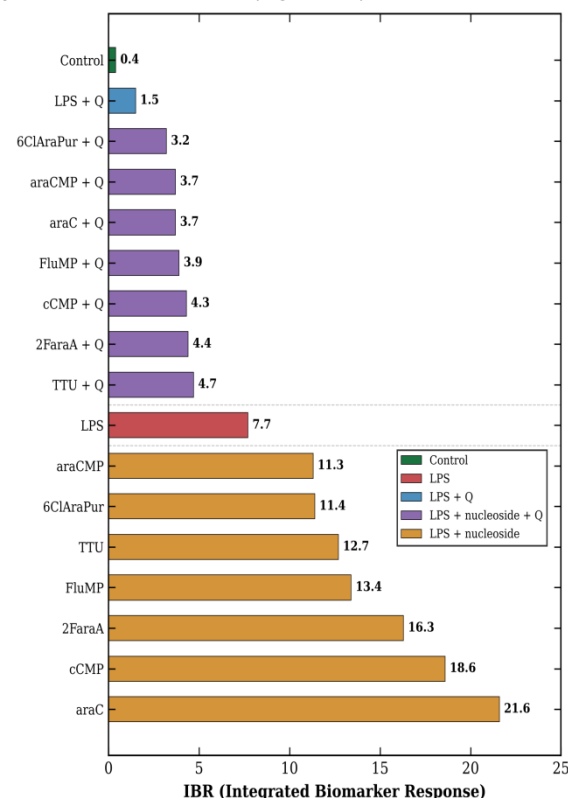


Figure 01: Ranked Integrated Biomarker Response (IBR) across all 17 experimental groups; values are annotated on the bars. The seven LPS + nucleoside groups (amber) occupy the high-burden pole above the LPS-only baseline (7.70); quercetin co-treatment (purple) returns every pair toward the control and LPS + Q references (green/blue).

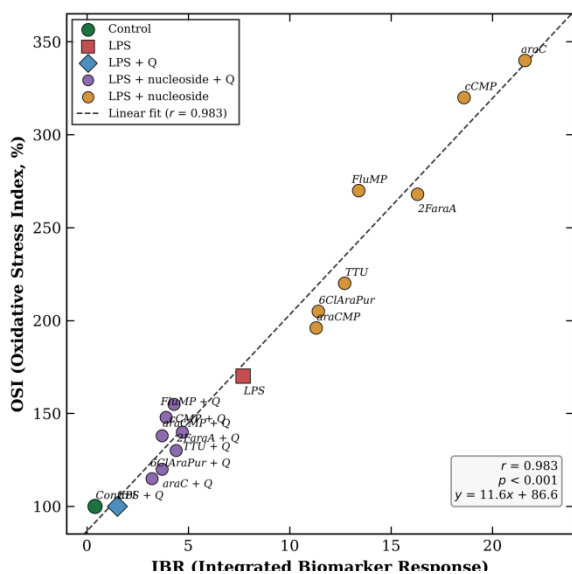


Figure 02: Correlation between the Integrated Biomarker Response and the Oxidative Stress Index across the 17 groups (linear fit, Pearson $r = 0.983$). Two indices derived by independent mathematical routes rank the groups identically, confirming the robustness of the IBR ordering.

3.3. Quercetin produced a consistent, class-independent redox recovery

Co-administration of quercetin restored the IBR toward the control value in every member of the chemical series. The recovery, expressed as the fraction of the distance from the LPS + nucleoside state back to naive control that is traversed when quercetin is added, ranged from 64.9 % (TTU) to 84.3 % (araC), with a mean of 74.4 % (Figure 3). Notably, the largest absolute rescue was obtained precisely where the burden was greatest: for araC the IBR fell from 21.57 to 3.73 (a deviation reduction of 17.84 units), and for cCMP from 18.57 to 4.25 (14.31 units). All seven recovery values fell within a single 20-percentage-point band, a remarkably narrow range given the structural diversity of the series. The uniformity of recovery across structurally distinct purines, pyrimidines and phosphorylated and cyclic nucleotides indicates that the quercetin benefit operates through a shared host antioxidant mechanism rather than through compound-specific chemistry.

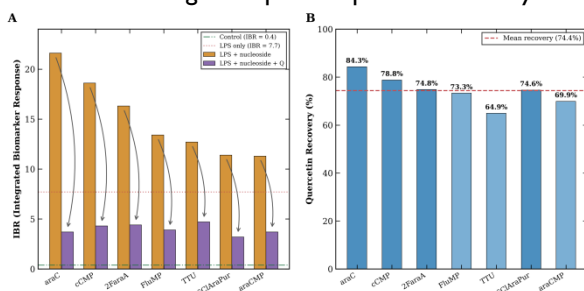


Figure 03: Quercetin-mediated restoration of the Integrated Biomarker Response. (A) IBR of each LPS + nucleoside group (amber) and its LPS + nucleoside + quercetin counterpart (purple), with arrows indicating the direction of recovery; control and LPS-only

reference lines are shown. (B) Recovery magnitude per compound; all seven values lie within a single 20-percentage-point band around the mean of 74.4 % (dashed line).

3.4. A single oxidative-burden axis explains group separation (PCA)

Principal-component analysis of the 17×17 group-by-marker matrix concentrated 80.2 % of the total variance in the first principal component, with a further 8.1 % in PC_2 (88.2 % cumulative). This unimodal variance structure means that the seventeen experimental groups are separated almost entirely along a single latent dimension that can be read as an oxidative-burden axis: the control and LPS + Q groups anchor the low-burden pole, the nucleoside-only groups occupy the high-burden pole in the same order as their IBR rank, and every nucleoside + quercetin group is displaced back toward the control pole (Figure 4). The clear spatial separation between the nucleoside-only cluster and the nucleoside + quercetin cluster, visible as two non-overlapping convex hulls, provides independent multivariate confirmation that quercetin shifts the redox profile toward the healthy baseline. This collapse of a 17-marker space onto essentially one interpretable axis is the multivariate counterpart of the IBR ranking and reinforces its robustness.

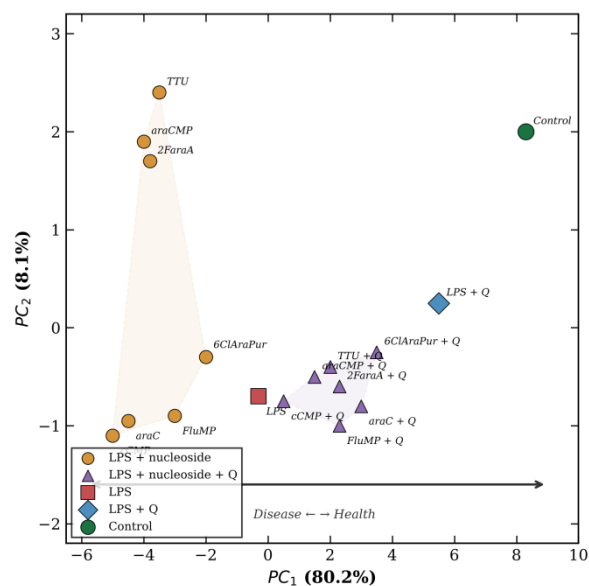


Figure 04: Principal-component scores of the 17 groups on the in vivo redox + haematology matrix.

PC_1 (80.2 %) is a disease-to-health axis: the naive control and LPS + Q groups lie at the healthy pole, the LPS + nucleoside groups at the diseased pole, and the LPS + nucleoside + quercetin groups at intermediate positions. Shaded hulls enclose each cluster.

3.5. The quercetin effect is carried by antioxidant enzymes, not by AST

ROC analysis identified which markers drive each contrast. For control vs LPS, the lipid-peroxidation and systemic markers TBARS, BUN, total protein, chloride, lymphocytes, H_2O_2 and HCT were maximally discriminating (directed AUC = 1.0), confirming a

broad inflammatory lesion. For the therapeutically central pooled contrast – nucleoside vs nucleoside + quercetin – the markers most sensitive to quercetin were the antioxidant enzymes GPX (AUC = 0.86), GSH (0.83) and SOD (0.81), together with TBARS (0.93). In contrast, serum AST did not differ significantly across the 17 groups (Kruskal–Wallis $H = 12.2$, $p = 0.73$) and was a poor discriminator of the quercetin effect (directed AUC = 0.58). This dissociation is mechanistically informative: quercetin selectively re-tunes the enzymatic redox-defence network that the nucleosides suppress, without normalising hepatocellular-leakage markers such as AST. The benefit is therefore redox-specific rather than a non-specific hepatoprotection (Table 03).

Table 03. Directed ROC AUC for three contrasts. Antioxidant enzymes (GPX, GSH, SOD) and TBARS best track the quercetin effect; AST does not, indicating redox-specific rather than generalised protection. AUCs derive from resampled animal-level data (see Methods).

Marker	Control vs LPS	LPS vs LPS + Q	Nucleoside vs + Q
GPX	0.92	0.92	0.86
GSH	0.92	0.84	0.83
SOD	0.80	0.64	0.81
TBARS	1.00	0.96	0.93
H ₂ O ₂	1.00	0.92	0.74
AST	0.80	0.80	0.58

4. DISCUSSION

Three findings emerge from compressing a 17-group, 17-marker in vivo dataset into integrative indices. First, modified nucleoside analogues do not impose a uniform redox cost when superimposed on inflammation: they rank reproducibly, with the cytarabine-type pyrimidines araC and cCMP carrying roughly twice the integrated oxidative burden of the least pro-oxidant member, araCMP. The fact that the IBR and a mechanistically independent OSI agree to within a correlation of 0.983, and that PCA places 80 % of the variance on a single axis that orders the groups identically, gives the ranking unusual internal consistency for an in vivo study. For antibacterial development this matters because it converts a wall of marker tables into a single actionable safety metric on which candidates can be triaged. A medicinal-chemistry programme could, for instance, use the IBR as a quantitative gate: analogues whose IBR exceeds a pre-set threshold under LPS challenge would require structural modification or mandatory co-treatment before advancing to efficacy trials. Second, quercetin produces a remarkably even redox rescue – 64.9 to 84.3 %, mean 74.4 % – across purines, pyrimidines, a monophosphate and a cyclic nucleotide. A protector whose effect were tied to the chemistry of each xenobiotic would vary widely across so diverse a series; the observed uniformity instead points to a host-side mechanism. Quercetin is an established activator of the Keap1–Nrf2/ARE axis [12–15], the master transcriptional regulator that induces SOD,

CAT, GPX and glutathione-system genes – precisely the enzymes our ROC analysis flags as the markers most responsive to co-treatment. That the largest absolute recovery occurs for the most pro-oxidant compound (araC) is consistent with a defence system being driven hardest where the oxidative challenge is greatest. This dose–response-like relationship between burden and recovery strengthens the mechanistic case for Nrf2-mediated induction as the principal protective pathway.

Third, the benefit is redox-specific. Serum AST, a marker of hepatocellular membrane leakage rather than of enzymatic redox tone, neither separated the groups ($p = 0.73$) nor responded to quercetin, even as GPX, GSH and SOD recovered. This dissociation cautions against interpreting quercetin co-treatment as blanket hepatoprotection: it restores the antioxidant-enzyme network without necessarily reversing structural hepatocellular injury, a distinction of direct relevance to safety framing in any future therapeutic combination.

These in vivo rankings dovetail with the wider mechanistic picture of this compound series. Our companion work showed that the bacteriostatic potency of the same analogues is largely ROS-independent [23], implying that their antibacterial action and their host oxidative cost are separable properties – an encouraging premise for a protector strategy that dampens the latter without, in principle, blunting the former. The present integrative analysis adds the systemic dimension: it ranks the host oxidative liability of each candidate and shows that a cheap, food-derived flavonoid neutralises about three-quarters of it across the board. Taken together, the in vitro efficacy data and the present in vivo safety ranking converge on a testable translational hypothesis: lower-burden analogues such as araCMP could be paired with quercetin in a combination regimen that preserves antibacterial potency while keeping the systemic oxidative cost within an acceptable margin.

The study has limitations. The per-group sample size ($n = 5$) is small, and the animal-level values underlying the ROC and Kruskal–Wallis statistics were reconstructed by parametric resampling from group summaries; those inferential figures should be read as descriptors of group separability rather than diagnostic-accuracy estimates. The IBR, OSI and PCA results, which rest on the measured group means, are not affected by this assumption. The mechanistic attribution to Nrf2/ARE is inferential within this dataset and is addressed directly elsewhere in our bioinformatic and docking work. Finally, the indices rank relative, not absolute, risk; dose-ranging and longer schedules would be needed to translate the ordering into therapeutic margins.

5. CONCLUSION

Applied to a full 17-group factorial dataset, the Integrated Biomarker Response and the Oxidative Stress Index rank seven modified nucleoside analogues by the systemic oxidative burden they add to LPS-

induced inflammation, identifying araC and cCMP as the most pro-oxidant and araCMP as the least. Quercetin co-treatment restores the integrated redox response toward control by a consistent 64.9–84.3 % (mean 74.4 %) across the entire chemical series, with the recovery carried by the antioxidant enzymes GPX, GSH and SOD and not by serum AST. The integrative framework – IBR, OSI, PCA and ROC in concert – provides a compact, reproducible safety-screening read-out for nucleoside-based antibacterial development, and the data support quercetin as a rational, low-cost redox-protective adjunct whose benefit is class-independent and mechanistically attributable to the host Nrf2/ARE pathway.

6. ETHICS

All animal procedures complied with institutional guidelines for the care and use of laboratory animals and were approved by the institutional ethics committee.

7. FUNDING

This research received no external funding.

8. COMPETING INTERESTS

A. A. Shihad is a member of the editorial board of the American Journal of Bioscience and Clinical Integrity. To preserve the integrity of the review process, the author declares this affiliation and confirms that he had no role in the peer review or editorial decision concerning this manuscript, which was handled independently by other editors. The authors declare no other competing interests.

9. AUTHOR CONTRIBUTIONS

A. A. Shihad: conceptualisation, investigation, data curation, writing – original draft. A. G. Syasa: supervision, methodology, formal analysis, writing – review and editing. Both authors approved the final version.

10. DATA AVAILABILITY

The biomarker tables and the analysis pipeline (IBR/OSI, PCA, ROC) are available from the corresponding author on reasonable request.

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