Journal of
Translational Regenerative Medicine

2026. Volume 1

Research Paper

Comparative Impact of Curcumin and Metformin on Reactive Oxygen Species Production and Antioxidant Gene Expression in T Cells

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Citation Mamivand A, Chamanara M, Mahboubian A, Saberian A, Mirjani R, Hami Z, et al. Comparative Impact of Curcumin and Metformin on Reactive Oxygen Species Production and Antioxidant Gene Expression in T Cells. Journal of Translational Regenerative Medicine. 2025; 1:E1001. http://dx.doi.org/10.32598/JTRM.1.1001

http://dx.doi.org/10.32598/JTRM.1.1001

ABSTRACT

Background: Excessive production of reactive oxygen species (ROS) is implicated in the pathogenesis of inflammatory and autoimmune disorders, partly through the dysregulation of T cell function. Curcumin and metformin possess well-documented antioxidant and anti-inflammatory properties, yet their combined effects on T cell oxidative stress have not been comprehensively evaluated.

Methods: Human peripheral blood T cells from healthy donors were treated with curcumin, metformin, or their combination. Intracellular ROS, superoxide, and glutathione (GSH) levels were quantified by flow cytometry. mRNA expression of key oxidative (NOX2) and antioxidant genes (*CAT*, *SOD1*, *SOD2*, *NRF2*) was assessed by quantitative reverse transcription polymerase chain reaction (qRT-PCR).

Results: Both agents significantly decreased ROS levels and increased intracellular GSH compared with untreated cells. Metformin exhibited superior effects, reducing ROS by ~2.5-fold and increasing GSH nearly 3-fold compared to curcumin. Metformin also induced stronger upregulation of *NRF2* and *SOD2*, and greater suppression of *NOX2*. Co-treatment produced no general synergistic effects on ROS, GSH, or most antioxidant genes, except for a significant synergistic increase in *SOD1* expression.

Conclusion: Metformin outperformed curcumin in enhancing antioxidant defenses and suppressing ROS in T cells, whereas combined therapy showed limited interaction, confined to *SOD1*. These findings support metformin—alone or with curcumin—as a potential candidate for managing oxidative stress–driven immune disorders, warranting further in vivo and clinical evaluation.

Keywords: Oxidative stress, Reactive oxygen species (ROS), Metformin, Curcumin, T cells

Article info:
Received: 05 Oct 2025
Accepted: 10 Dec 2025
Publish: 13 Jan 2026

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Highlights

- Metformin exhibited superior effects on reducing ROS levels and increasing intracellular GSH compared to curcumin.
- Metformin induced stronger upregulation of *NRF2* and *SOD2*, and greater suppression of *NOX2* compared to curcumin.
- Combined curcumin-metformin therapy could cause a significant increase in *SOD1* expression.
- Metformin (alone or with curcumin) is a potential candidate for managing oxidative stress.

Plain Language Summary

Although reactive oxygen species (ROS) are vital for maintaining normal cellular activities, an imbalance between their production and elimination can lead to oxidative stress, which can develop several diseases, including neurodegenerative disorders, cardiovascular diseases, cancer. In this study, we focused on how curcumin and metformin influence the expression of enzymes involved in ROS production within T cells. We examined the effect of combining curcumin and metformin for conditions characterized by heightened inflammatory responses and oxidative stress. The results showed that both agents significantly reduced ROS levels and increased intracellular GSH compared with untreated cells. However, metformin outperformed curcumin in enhancing antioxidant defenses and suppressing ROS in T cells. Their combination only caused a significant increase in SOD1 expression. Overall, it can be concluded that metformin—alone or with curcumin—is a potential candidate for managing oxidative stress–driven immune disorders, warranting further in vivo and clinical evaluation.

Introduction

Reactive oxygen species (ROS) are highly reactive molecules containing oxygen that are generated naturally as byproducts of cellular metabolism. They are primarily produced by the electron transport chain in mitochondria and the cytochrome P450 system. Additionally, a significant source of ROS originates from NADPH oxidases expressed in various cell types, particularly in professional phagocytes and endothelial cells, where their dysregulation contributes to vascular pathology and oxidative stress [1, 2]. These enzymes are crucial in initiating the inflammatory response [3]. Besides their involvement in inflammation, ROS play essential roles in numerous physiological processes, including cell signaling and immune system function [4, 5].

While ROS are vital for maintaining normal cellular activities, an imbalance between their production and elimination can lead to oxidative stress. This imbalance can damage critical cellular components, including proteins, lipids, and DNA. Consequently, oxidative stress is implicated in the development of several diseases, including neurodegenerative disorders, cardiovascular diseases, cancer, and autoimmune conditions [6-8]. To combat ROS, cells employ intricate defense mechanisms that include antioxidative enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) peroxidase, as well as non-enzymatic antioxidants such as vitamins C and E, which collectively help maintain the balance between ROS production and elimination [9, 10].

In the context of inflammation, ROS serve a dual purpose. They act as signaling molecules essential for host defense against pathogens, but can also contribute to tissue damage when their levels become excessive or dysregulated. Maintaining a precise balance of ROS is therefore critical, as excessive ROS can lead to chronic inflammation and significantly contribute to the pathogenesis of various inflammatory diseases. Current research focuses on unraveling the complex regulatory mechanisms that control ROS levels to develop targeted therapeutic strategies for inflammatory disorders [11, 12].

T lymphocytes are central to the adaptive immune system, orchestrating responses to pathogens, allergens, and tumors throughout an individual's life [13, 14]. For their proliferation and functional responses, T cells depend on multiple metabolic pathways to generate sufficient ener-

gy and metabolites. These metabolic activities, however, often result in the production of ROS. Emerging studies have identified ROS as vital secondary messengers in T cell receptor signaling and activation, although their effects can vary across different T cell subsets. Therefore, the precise regulation of ROS production through cellular antioxidant mechanisms is essential to ensure accurate signaling and effective T cell responses [15].

Numerous studies have explored the impact of curcumin on ROS metabolism and inflammation. Curcumin, a compound renowned for its antioxidant properties, effectively scavenges ROS, including superoxide anions and HO [16, 17]. It also enhances the activity of key antioxidant enzymes, such as SOD and CAT, which are fundamental in protecting the body against oxidative stress. Due to its potent anti-inflammatory and antioxidant effects, curcumin has gained considerable attention as a potential therapeutic agent for chronic inflammatory diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease, with various studies investigating its efficacy in these conditions [8, 18, 19].

Similarly, metformin is being studied for its potential effects on ROS and oxidative stress [20]. Metformin primarily functions by activating AMP-activated protein kinase (AMPK), a critical regulator of cellular energy homeostasis. Activation of AMPK leads to multiple downstream effects, including the suppression of hepatic gluconeogenesis, increased glucose uptake in peripheral tissues, and maintenance of intracellular energy balance. Notably, evidence suggests that metformin's antioxidant effects may be linked to AMPK activation [21, 22]. This mechanism may play a significant role in managing oxidative stress at the cellular level, providing insights into metformin's broader implications in reducing inflammation. These findings indicate that metformin may help lower oxidative stress, supported by scientific studies demonstrating its beneficial effects.

In this study, we examine the antioxidant effects of curcumin and metformin on the redox system in T cells. While previous research has investigated the impact of these two drugs on the redox systems of various tissues, their combined effects on the immune system, particularly on T cells, remain unexplored. Therefore, we focused on how curcumin and metformin influence the expression of enzymes involved in ROS production within T cells. Specifically, our investigation highlights how the combination of these drugs enhances the expression of antioxidative genes, including *CAT*, nuclear factor erythroid 2-related factor 2 (*NRF2*), and SOD (*SOD1* and *SOD2*), which are crucial for degrading ROS and mitigating oxidative stress. Concurrently, the treatment suppresses NADPH oxidase 2 (*NOX2*) expression, a gene directly involved in ROS generation. Using flow cytometry, we quantitatively assess changes in ROS, superoxide anion (O_2^-), and GSH levels in T cells following treatment, thereby corroborating the genetic expression data with empirical evidence of reduced oxidative stress. This research proposes a potential therapeutic strategy combining curcumin and metformin for conditions characterized by heightened inflammatory responses and oxidative stress, providing a molecular basis for their use by modulating ROS dynamics in immune cells.

Materials and Methods

Cell culture

Blood was obtained from healthy donors, and human peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll–Paque density gradient centrifugation. These isolated PBMCs were then placed in 24-well plates (1.5×10^6 cells/well) and cultured in RPMI 1640 with 10% FBS and 100 IU hIL-2 (Miltenyi Biotec). To enrich T cells, PBMCs were cultured with 3 µg/mL anti-CD3 (Miltenyi Biotec) and 10 µg/mL anti-CD28 (Miltenyi Biotec) antibodies.

Flow cytometry and ROS assay

ROS and superoxide detection assay kits (ab139476, USA) were utilized to assess intracellular ROS production levels. T cells (2×10^5 cells per well) were cultured in RPMI1640 complete media with or without curcumin, metformin, and metformin/curcumin co-treatment (7 mM). Following harvesting and washing, the cells were exposed to a permeable green probe (responsive to hydroxyl radicals [HO], hydrogen peroxide (H_2O_2), peroxynitrite [$ONOO^-$], peroxy radical [ROO], and nitric oxide [NO]) and an orange probe (specifically reactive to superoxide [O_2^-]) at 37 ˚C for 30 minutes. The GSH antioxidant level was determined using a GSH assay kit (ab112132, USA). After harvesting and washing, the cells were treated at 24 ˚C with thiol green dye for 20 minutes. Subsequently, flow cytometry was employed for cell analysis. ROS/superoxide and GSH production were determined by measuring the difference in mean fluorescence intensity (MFI) between treated and untreated cells. Flow cytometry was performed using a BD FACS Calibur (BD Biosciences, USA) and analyzed using FlowJo software, version 7.6.1 The experiments were carried out in triplicate and replicated three times.

Table 1. Primers used for gene expression analysis through real-time PCR

Gene Name	Forward Primer	Reverse Primer	Size (bp)
NOX2	CTGGAAACCCTCCTATGACTTG	GTGATGACCACCTTCTGTTGAG	106
CAT	TGCTGAATGAGGAACAGAGGAA	CCTCACAGATTTGCCTTCTCC	238
NRF2	CCATTCCTGAGTTACAGTGTCT	CTGTGGAGAGGATGCTGC	204
SOD1	AGCGAGTTATGGCGACGAAG	CAGCCTGCTGTATTATCTCCA	181
SOD2	CTCAGGTTGGGGTTGGCT	TGAAGGTAGTAAGCGTGCTCC	144
18s rRNA	GTAACCCGTTGAACCCCATT	CCATCCAATCGGTAGTAGCG	151

Abbreviations: NOX2: NADPH oxidase 2; *CAT*: Catalase; *NRF2*: Nuclear factor erythroid 2-related factor 2; *SOD1*: Superoxide dismutase 1; *SOD2*: Superoxide dismutase 2.

RNA extraction and cDNA synthesis

TriPure isolation reagent (Roche, Mannheim, Germany) was used for RNA extraction, according to the protocol. RNA concentration was quantified with the NanoDrop-2000 spectrophotometer (Thermo Fisher, U.S) and sorted at -70 ˚C. cDNA synthesis using 1 µg of total RNA and PrimeScript RT reagent (Takara Bio Inc., Shiga, Japan) was performed according to the protocol.

Quantitative reverse transcription polymerase chain reaction

Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was carried out using the SYBR Premix Ex TaqTM according to a previous study [23]. First, primers were designed using Oligo 7, and their specificity was checked using Primer-BLAST. Primer sequences were listed in Table 1. All primers were designed on exon-exon junctions or had an intron larger than 2000 nucleotides between them to prevent amplification of genomic DNA contamination (if any). The melting curve was also analyzed to confirm the primers' specificity. A serial dilution was prepared, and PCR conditions were adjusted to achieve a PCR efficiency of 2. The qRT-PCR reaction was performed according to the following conditions: incubation for 10 min at 95 ˚C, followed by 40 cycles of elongation, including 10s at 95 ˚C and 25 s at 60 ˚C. To exclude primer dimers or byproducts, dissociation curves were carefully analyzed to assess the specificity of the product melting peak. The PCR products were ultimately confirmed by 2% agarose gel electrophoresis.

Statistical analysis

Superoxide and GSH levels in CD4+ T cells between the treated and untreated groups were compared using a one-way analysis of variance (ANOVA) followed by a Tukey post hoc test. The Wilcoxon test was used to assess differences in expression between groups. A $P<0.05$ was deemed statistically significant for a confidence interval of 95%. Statistical analysis was performed using GraphPad Prism software, version 8.

Results

Curcumin treatment and significant antioxidant effects on T cells

Flow cytometry analysis revealed that curcumin treatment markedly reduced intracellular ROS levels in activated T lymphocytes compared with untreated controls (Figure 1A). The MFI for ROS decreased substantially, indicating a significant attenuation of oxidative stress. Although a mild decrease in superoxide (O_2^-) production was observed, this change did not reach statistical significance. Conversely, intracellular GSH levels rose significantly following curcumin administration (Figure 1B), suggesting enhanced antioxidant capacity.

Gene expression analysis by qRT-PCR showed significant upregulation of key antioxidant enzymes—*CAT*, *SOD1*, and *SOD2*—in curcumin-treated cells. While *NRF2* expression exhibited an upward trend, it did not reach statistical significance. Importantly, curcumin significantly downregulated *NOX2* expression, a critical ROS-generating enzyme, consistent with the observed reduction in oxidative stress (Figure 1C).

Metformin treatment demonstrates significant antioxidant effects on T Cells

Metformin treatment resulted in a pronounced reduction in ROS levels in T lymphocytes, surpassing the effect observed with curcumin (Figure 2A). The MFI for

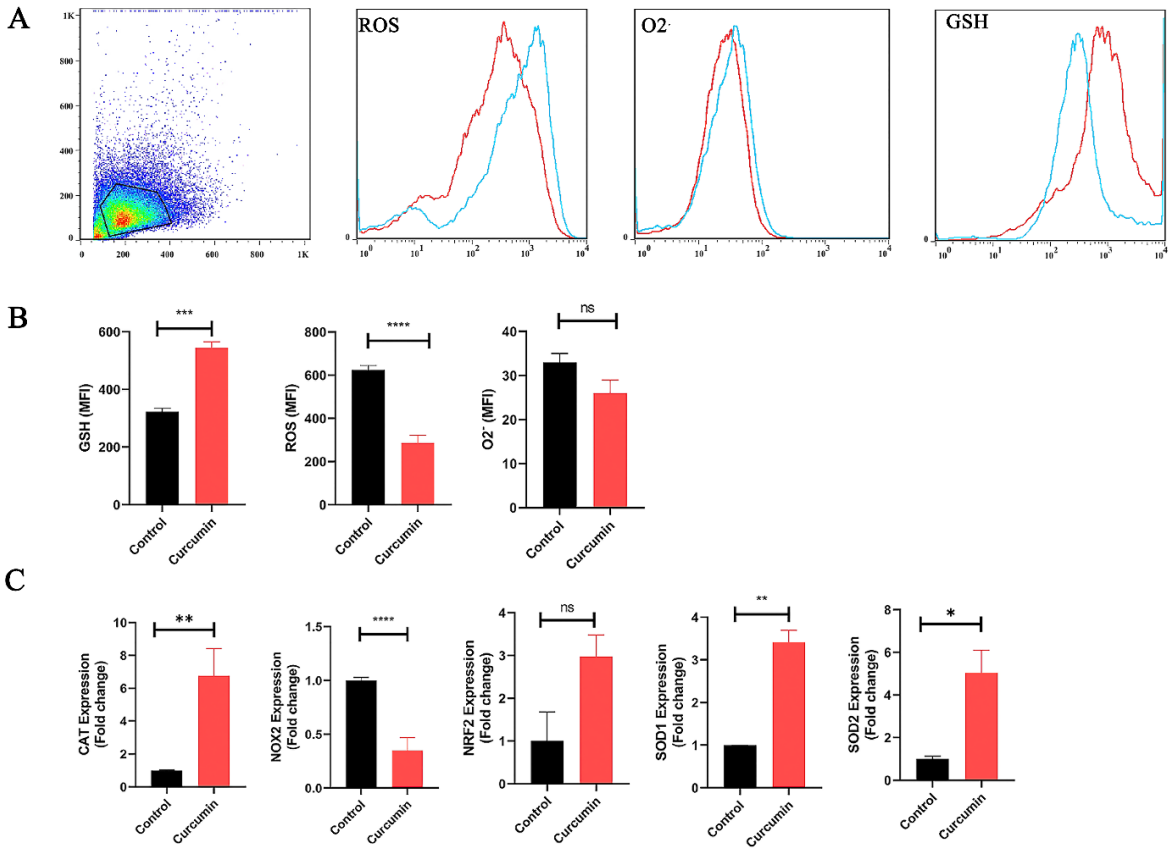

Figure 1. A) and B) ROs production in T cells decreased after curcumin treatment; C) Antioxidant (CAT, NRF2, SOD1, SOD2) and oxidant (NOX2) enzymes upregulated and downregulated after treatment, respectively

Note: The decrease in O_2^- production was not significant (P=0.12). However, the elevation in *NRF2* expression did not reach statistical significance (P=0.2).

ROS in metformin-treated cells (108) was approximately 2.5-fold lower than that of curcumin-treated cells (286). GSH levels increased significantly, nearly three-fold higher with metformin (1494 MFI) compared to curcumin (544 MFI) (Figure 2B). Superoxide production showed a slight but statistically nonsignificant decrease.

At the molecular level, metformin significantly upregulated CAT, SOD1, SOD2, and NRF2. Moreover, metformin markedly suppressed NOX2 expression to a greater extent than curcumin (Figure 2C). Collectively, these data indicate that metformin exerts more potent antioxidant effects on T cells, both by enhancing antioxidant defence genes and by more effectively inhibiting prooxidant gene expression.

Co-treatment with metformin and curcumin does not demonstrate synergistic effects

When both drugs were applied simultaneously, ROS levels decreased significantly and GSH levels rose compared with untreated cells (Figure 3A), mirroring the trends seen with single-agent treatments. However, the magnitude of change was comparable to metformin alone, and no statistically significant difference was observed in ROS or GSH levels relative to either monotherapy. Superoxide production showed a slight, non-significant rise compared with monotherapy groups (Figure 3B).

Gene expression profiling revealed that combined treatment induced increases in *CAT*, *SOD1*, *SOD2*, and *NRF2*, and suppressed *NOX2*, resembling the patterns observed with the individual treatments (Figure 3C). Notably, SOD1 was the only antioxidant enzyme to show a significant synergistic increase under co-treatment, suggesting a specific but limited additive effect.

Comparative analysis across treatment groups

Direct comparison of the three experimental groups—curcumin, metformin, and their combination—con-

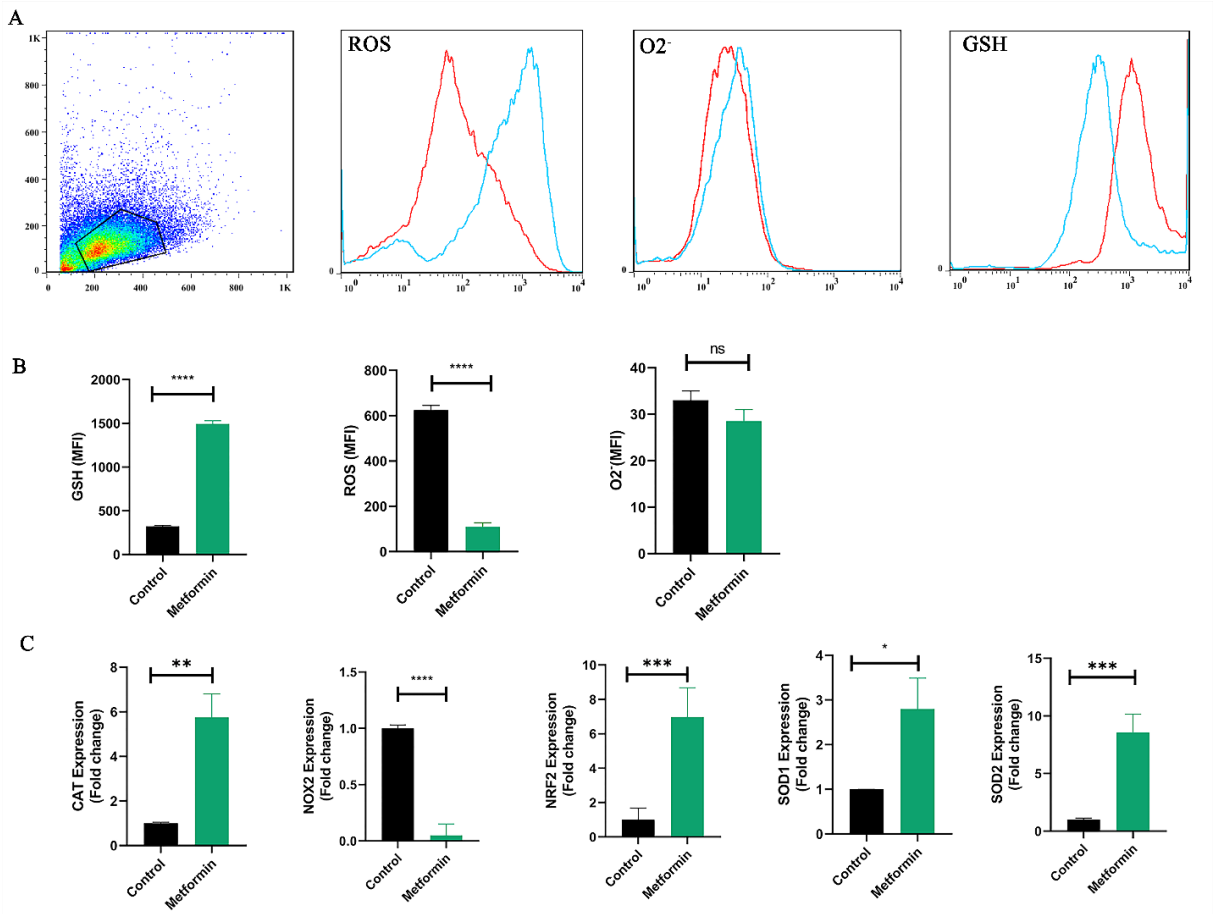

Figure 2. A) and B) Metformin treatment significantly reduced ROS production in T cells, while O_2^- levels without change significantly (P=0.4); C) The increased expression of antioxidant enzymes after treatment of T cells with metformin

Note: On the other hand, NOX2, one of the main ROS-producing enzymes, was significantly downregulated after treatment.

firmed metformin's superior efficacy in lowering ROS and boosting GSH levels (Figure 4A). ROS production in curcumin-treated cells (286 MFI) was approximately 2.5 times higher than in metformin-treated cells (108 MFI). GSH levels were almost three times higher in the metformin group (1494 MFI) than in the curcumin group (544 MFI). *NRF2*, *SOD2*, and *NOX2* expression differed significantly between curcumin and metformin groups, favoring metformin. In contrast, *CAT* and *SOD1* levels were slightly higher with curcumin, but the difference was not statistically significant. As expected from the gene-level data, the only clear collaboration in the co-treatment group was observed for *SOD1* expression (Figure 4B).

Discussion

In this study, we examined the antioxidant effects of curcumin and metformin on T cells, with a particular focus on their ability to modulate ROS production and alter the expression of key genes involved in ROS metabolism. Our results clearly demonstrate that both agents significantly reduced intracellular ROS levels—as evidenced by decreased fluorescence intensity in flow cytometry assays—with metformin-treated T cells exhibiting approximately 2.5-fold lower ROS fluorescence (108 MFI) than curcumin-treated cells (286 MFI). Both treatments enhanced intracellular antioxidant capacity by increasing GSH levels, though metformin induced a nearly three-fold greater rise than curcumin (1494 MFI vs 544 MFI). This stronger effect may be linked to metformin's potent activation of AMPK and its consequent impact on upregulation of *NRF2* and *SOD2*, along with more substantial suppression of *NOX2* expression.

These findings fit within the broader context of ROS biology in immune cells. ROS play a dual role in immune function—facilitating pathogen eradication by damaging microbial membranes and DNA. At the same time, excessive accumulation can impair T cell function, intensify inflammation, and contribute to the development of autoimmune disorders [24]. Elevated ROS lev-

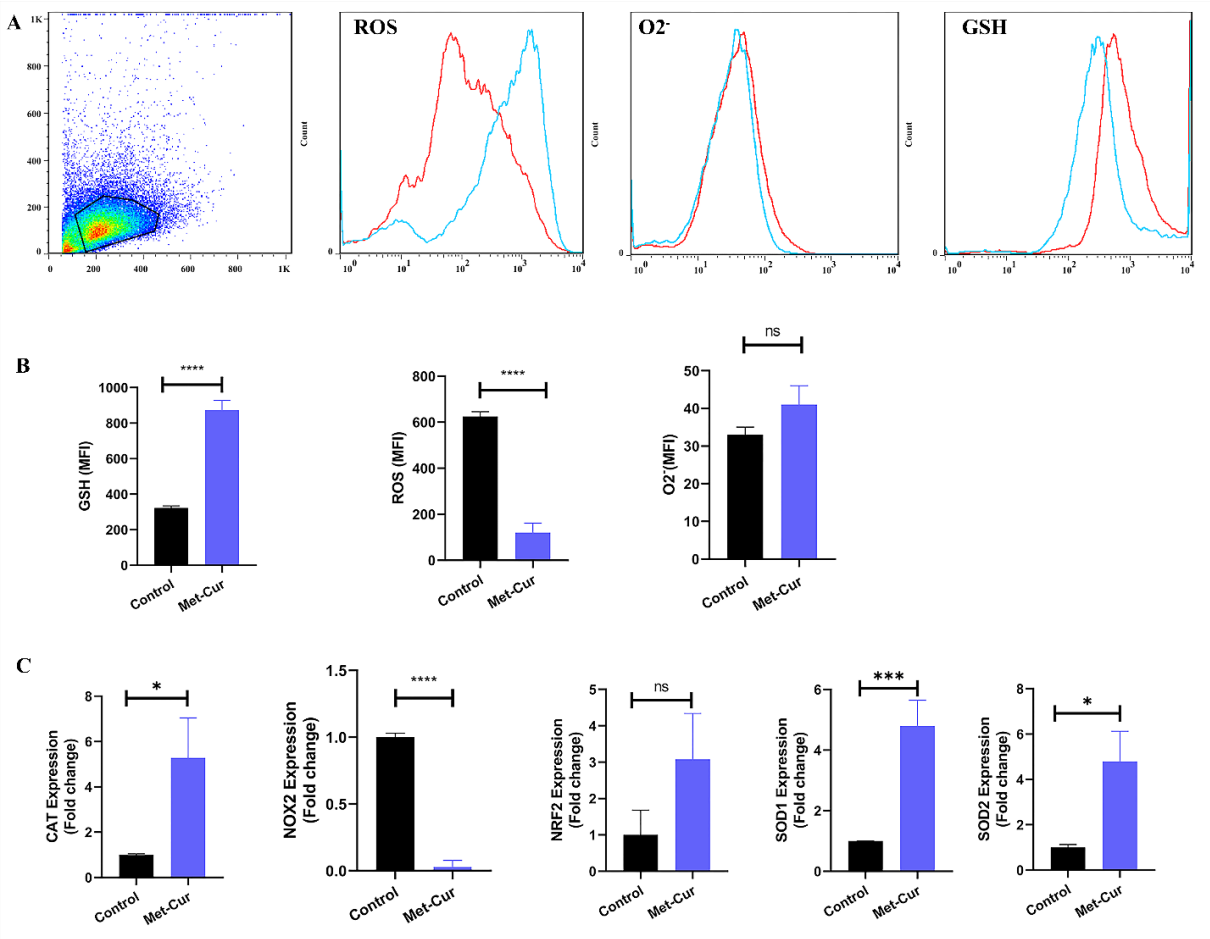

Figure 3. Metformin/curcumin co-treatment with antioxidant properties, like treatment with curcumin or metformin alone

els have been reported in diseases such as RA, multiple sclerosis (MS), and inflammatory bowel disease (IBD) [25-27]. For instance, IBD is characterized by abnormally high ROS levels in the colon, and increased ROS in T cells during relapse phases of MS has been documented, along with elevated expression of ROS-producing enzymes [25-27]. Therefore, agents that reduce ROS in T cells are likely to improve disease prognosis and attenuate pathological inflammation.

In our study, curcumin significantly decreased ROS levels in T cells and upregulated antioxidant enzymes *CAT*, *SOD1*, and *SOD2*, while *NRF2* expression increased but did not reach statistical significance. These observations align with previous research in other cell types, such as endothelial cells in diabetic patients, where curcumin treatment reduced *NOX2* expression—a key enzyme in ROS production [28]. Besides its antioxidant role, curcumin is well known for its anti-inflammatory effects, including inhibition of pro-inflammatory cytokines and chemokines and downregulation of inflammatory gene expression [29].

Consistent with its reported immunomodulatory properties, metformin in our study exhibited more potent antioxidant effects than curcumin. Compared with curcumin, metformin led to markedly greater suppression of *NOX2*, significant upregulation of *NRF2* and *SOD2*, and a nearly three-fold larger increase in GSH levels. Metformin has been shown to inhibit pro-inflammatory cytokines (interleukin-1 beta [IL-1β], IL-1β, IL-6, Tumor necrosis factor [TNFα]) and promote IL-10 expression in activated macrophages [30], as well as shift T cell differentiation towards regulatory T cells (Tregs) while suppressing Th1 and Th17 cell subsets via AMPK activation [30]. These mechanisms, in combination with its antioxidant activity, may explain the superior performance of this compound in reducing ROS in T cells observed here.

When comparing the two agents directly, a broadly similar pattern of antioxidant gene expression emerged. Still, the magnitude of change differed substantially, favoring metformin for ROS suppression, GSH en-

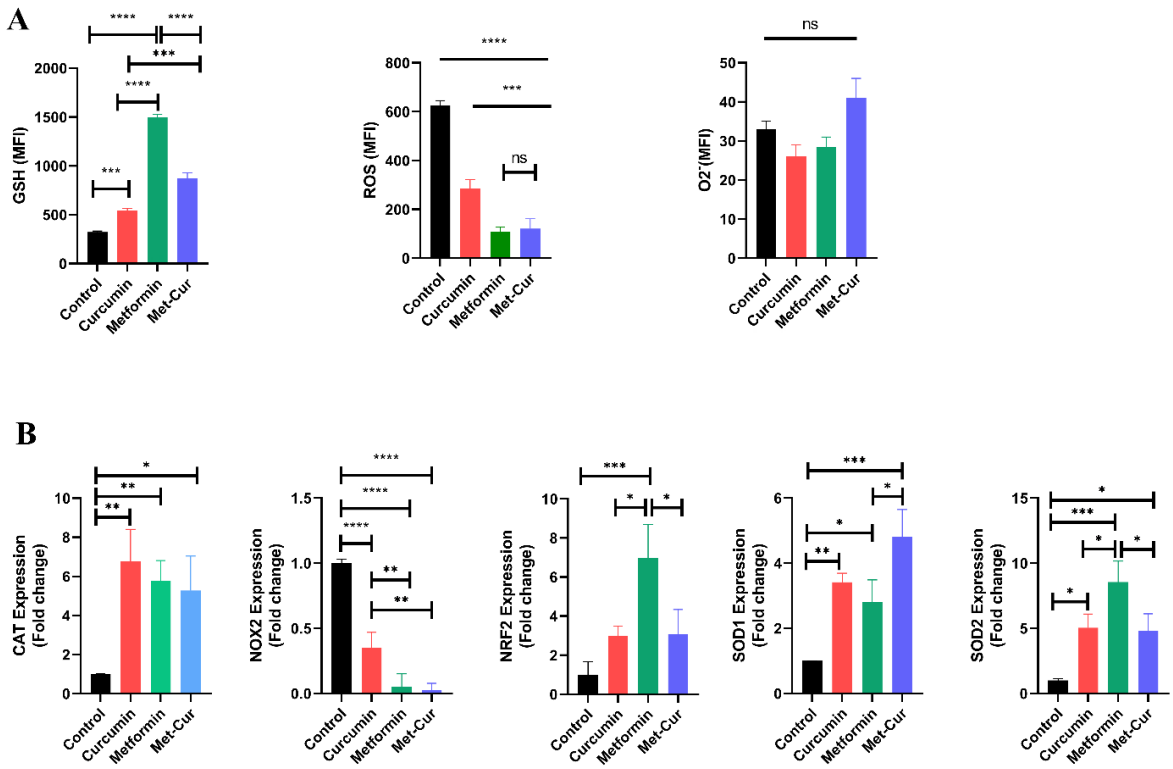

Figure 4. The co-treatment of metformin and curcumin without a synergistic effect in reducing the ROS production (A) and increasing the antioxidant enzymes expression (B)

hancement, *NRF2* and *SOD2* upregulation, and *NOX2* suppression. Co-treatment with both compounds did not produce synergistic effects for most measured outcomes. The sole exception was *SOD1* expression, which showed a statistically significant synergistic increase under combined treatment. This lack of broader synergy could indicate overlapping modes of action or saturation of shared signaling pathways, such as those mediated by AMPK or NRF2-dependent antioxidant responses.

It should be noted that these findings are based on in vitro T cell cultures, which may not fully replicate the complexity of immune responses in vivo. The lack of synergy across most parameters suggests that alternative dosing strategies, sequential administration, or formulation changes may be needed to maximize potential combinational benefits. Future studies involving in vivo models and clinical trials are necessary to validate these results and further investigate the molecular interplay between curcumin and metformin in regulating oxidative stress in immune-mediated disorders.

Conclusion

In conclusion, both curcumin and metformin reduced oxidative stress in human T cells by lowering ROS levels and enhancing antioxidant defenses. Metformin consistently outperformed curcumin, showing approximately 2.5-fold greater ROS suppression, nearly 3-fold higher GSH elevation, stronger upregulation of *NRF2* and *SOD2*, and more potent suppression of *NOX2* expression. While co-treatment with both compounds did not produce broad synergistic effects across ROS, GSH, or most antioxidant genes, *SOD1* expression emerged as a noteworthy exception, displaying a clear synergistic enhancement. These findings suggest that metformin, alone or in combination with curcumin, may be a promising therapeutic candidate for immune-related disorders characterized by elevated oxidative stress. Nevertheless, the lack of general synergy and the in vitro nature of this study underscore the need for further in vivo work and clinical evaluation to determine optimal therapeutic strategies and elucidate the molecular interactions underlying these effects.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization and study design: Ali Mamivand and Reza Heidari; Data collection, data analysis and interpretation, writing, and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to express their gratitude to the Central Research Laboratory at Aja University of Medical Sciences, Tehran, Iran, for providing the necessary resources and support for this research.

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