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Gas Station Heroin: Tianeptine's Immunomodulatory Effects on Central and Peripheral Tissues

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ABSTRACT

Purpose: Tianeptine, a tricyclic antidepressant targeting mu-opioid receptors, is approved in many countries but not in the U.S. While notorious for abuse risk, its immunomodulatory effects remain underexplored. This study examines: (1) dose-specific regulation of immune and inflammatory responses, and (2) effects across brain and peripheral immune cells.

Methods: We assessed cytotoxicity in RAW264.7 macrophages and SIM-A9 microglia using LDH assays across dilutions from 10 to 0.01953 µg/mL over 2 hours. After LPS challenge, baseline and post-/pre-treatment levels of TNF-α and IL-10 were measured via ELISA. Phagocytosis was evaluated by exposing cells to fluorescent E. coli and quantifying mean fluorescence intensity (FMI) as a measure of engulfment.

Results: Tianeptine exhibited a U-shaped cytotoxic profile in both cell types. Compared to LPS controls, IL-10 expression rose significantly while TNF-α levels dropped ~8-fold. Microglia (SIM-A9) showed greater IL-10 release than macrophages at equivalent doses; both exhibited comparable TNF-α suppression. Pre- and post-treatment with tianeptine further reduced inflammatory cytokines. Notably, phagocytic activity declined dose-dependently in RAW264.7 cells but increased in microglia.

Conclusions: These data reveal divergent immunomodulatory effects of tianeptine between peripheral macrophages and central microglia, with biphasic cytotoxicity and differential phagocytic responses. Future research should aim to clarify the receptor specific mechanisms of tianeptine's immunomodulatory effect including the contributory factor of µ-opioid receptor signaling, and immunological consequences that may be relevant to the safety of tianeptine. Ultimately, this work adds more context to the expanding field of research investigating the immunological effects of psychiatric medications.

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Introduction

The ongoing opioid epidemic, with increasing restrictions on prescription opioids, has driven some individuals to seek alternative substances for pain relief or euphoria. Tianeptine is an atypical tricyclic antidepressant (TCA) which also acts as a µ-opioid receptor (MOR) agonist, that rose in popularity in the mid-2010s and continues to be increasingly misused in the United States. Known colloquially as "gas station heroin", "Zaza", or "Tianna Red," tianeptine is prone to abuse due to its euphoric effects and rapid tolerance when taken at doses well above the therapeutic level [1]. First developed in France in the 1960s, tianeptine has been used for the treatment of major depressive disorder (MDD) in many countries. In the United States, it is not approved by the FDA, however, tianeptine is commonly sold in gas stations, convenience stores, and smoke shops, in which its sale is not tightly regulated in several states. Despite its historical clinical use in other countries, tianeptine has become the subject of growing concern due to its increasing misuse and abuse, particularly in the United States.

The Centers for Disease Control and Prevention estimates that there were over 100,000 drug overdose deaths in the United States in 2024, including more than 75,000 deaths from opioids [2]. Tianeptine, is seen by some as an easily accessible alternative to other drugs such as heroin and prescription opioids. Another method of abuse is the use of tianeptine to relieve withdrawal symptoms from other opioids. In recent years there have been 8 confirmed fatalities involving tianeptine either alone or combined with other drugs of abuse [3,4]. Furthermore, in a 5-month period of 2023, in New Jersey, 17 individuals presented to healthcare facilities with illnesses related to tianeptine ingestion, many having consumed an elixir called "Neptune's Fix" containing the drug, marking a significant increase in events over previous years, in the state [5].

After its initial development, tianeptine was originally thought to enhance serotonin reuptake, the opposite mechanism of selective serotonin reuptake inhibitors. Tianeptine was first approved for medical use in France in 1989 under the brand name Stablon. In the early 2000s, the hypothesis that it enhanced serotonin reuptake was weakened, and it was not until 2014 that Tianeptine was discovered to be a full agonist at the μ-opioid receptor, a property now recognized as central to its abuse liability [6]. Due to tianeptine's enigmatic mechanism of action, safety concerns, and lack of superior efficacy to currently approved anti-depressants, it is not being considered for FDA approval. However, tianeptine's emerging role as a drug of abuse has brought it new relevance, warranting FDA warnings against tianeptine-containing products in 2023 [7].

Tianeptine is a derivative of dibenzothiazepine and features a tricyclic, lipophilic structure, allowing it to penetrate the blood-brain barrier. It is mainly metabolized by beta-oxidation of its 7-carbon side chain [6]. Although the precise mechanism of its underlying central nervous system effects remains incompletely understood. Tianeptine is a MOR agonist and has been shown to have effects on the neurotransmitter's serotonin, glutamate, and dopamine. It is typically administered orally, in tablet or liquid form, with a therapeutic dose of 12.5 mg taken three times daily in approved settings [8]. When taken at doses above therapeutic levels, its opioid-receptor activity leads to risks of tolerance and withdrawal.

Beyond its established psychotropic effects, recent research has shown that tianeptine plays a role in the immune response to inflammation. Studies have supported the involvement of neuroinflammation in the pathophysiology of depression and related neuropsychiatric disorders [9]. It has been shown that individuals suffering from depression often have elevated levels of pro-inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). These cytokines can affect the brain by altering neurotransmitter metabolism, neuroplasticity, and the hypothalamic-pituitary-adrenal (HPA) axis, all of which play an important role in mood regulation. Furthermore, an inflammatory state can decrease levels of serotonin, leading to a more depressed mood. For example, indoleamine 2,3 dioxygenase (IDO) is an enzyme that is increased in an inflammatory state, and its function is to break down tryptophan, a precursor to serotonin [10]. These observations support investigation into the mechanisms of tianeptines immunomodulatory effects.

Microglia are thought to be the main mediator of inflammation in the central nervous system. MORs are believed to be involved in immunosuppression. Activation of μ -opioid receptors suppresses the immune system by reducing natural killer cell activity, limiting the ability of T and B cells to respond to stimuli, decreasing antibody production, and impairing the function of neutrophils and macrophages. These immunosuppressive effects are directly caused by the μ -opioid receptor, as shown by studies where blocking or removing this receptor prevents opioid-induced immune suppression [11]. Tianeptine is shown in recent studies to suppress microglial activation in response to LPS, reducing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), nitric oxide, reactive oxygen species, and markers of microglial activation [12,13]. These findings make tianeptine an intriguing candidate for further research of its role in modulating inflammation.

Microglia and peripheral macrophages, the primary immune effectors in the central nervous system (CNS) and periphery, respectively, play an important role in mediating inflammation. The present study was designed to investigate the immunoregulatory effects of tianeptine on both central and peripheral immune macrophages. Due to tianeptine's classification as a psychotropic agent, with known activity at opioid receptors, we aim to compare tianeptine's potential role in immune regulation in the central nervous system with that in peripheral tissue by investigating murine RAW 264.7 macrophages and SIM-A microglia in vitro. The focus of the current study was to test the pro-inflammatory and anti-inflammatory cytokine expression, cytotoxicity, and phagocytic actions in both cell lines. By combining ELISA, LDH assays, and phagocytosis assays, the current study provides a comprehensive assessment of how tianeptine alters immune cell function, by testing whether tianeptine's effects extend beyond mood regulation to include modulation of innate immune responses. This study brings to light the contrast and similarities between immune response to tianeptine by microglia compared to tissue macrophages.

In the context of tianeptines increasing misuse throughout the United States, examination of its effects on immune signaling may provide valuable insight into biological consequences associated with exposure to tianeptines. Accordingly, this project is framed to seek out and discuss the relevance of tianeptine on neuroimmune biology and public health risk assessment, rather than as a basis for therapeutic use.

Materials and Methods

Cell Culture and Dose-Response Curves

Cells were regularly grown in T-75 cell culture flasks in DMEM or DMEM F12 medium (Gibco, Life Technologies) supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10 mM HEPES, 0.1 mM non-essential amino acids, 1.5 g/L sodium bicarbonate, 50 U/mL penicillin, and 50 mg/mL streptomycin. Murine peripheral macrophages (ATCC: RAW 264.7, TIB-71) and murine alveolar macrophage (ATCC: MH-S, CRL-2019) cells were seeded to wells in a 24-well plate. To study the drug effect on each cell line independently, dose-response curves were generated as follows. Cells were incubated in growth media supplemented with varying concentrations of tianeptine for 2 hours. The concentrations of tianeptine used were 10, 5, 2.5, 1.25, 0.625, 0.3125, 0.1563, 0.07813, 0.03906, 0.01953 ug/mL diluted in 500uL. Controls of PBS, vehicle DMEM, and vehicle DMEM F12 were included. After incubating, each sample was run in duplicate using the CyQUANT™ LDH Cytotoxicity Assay Kit (ThermoFisher Cat # C20300).

Inflammation

Tianeptine (Cayman Chemical, Item No. 17561) concentrations of 0.16, 0.32, 0.63, 1.25 ug/mL were selected for Raw 264.7 cell lines based on dose-response curve. Concentrations of 0.01, 0.02, 0.04, 0.078 ug/mL were selected for the microglial cell lines based on dose-response curve. Vehicle controls and 1 ug/mL of LPS were utilized (Cayman Chemical, Item No. 19660). Each sample was run in replicates of 4 and incubated for 2 hours. After incubation, each sample was processed using the Invitrogen Mouse TNF-alpha ELISA kit (Cat #88-7346-22) and the Invitrogen Mouse IL-10 ELISA kit (Cat #88-7106-22).

Pre-treatment and Post-treatment Tianeptine

The pre-treatment group was treated with tianeptine dissolved in the appropriate growth media and incubated at 37 degrees Celsius for 2 hours. Then the media was decanted, and the cells were treated with 1 ug/mL of LPS dissolved in growth media and incubated for 2 hours. The supernatant was then removed and

frozen at –80 degrees Celsius for later testing of IL-10 and TNF-a using the same ELISA methods as previously described. The post-treatment group was treated with 1 ug/mL of LPS dissolved in growth media for 2 hours. The solution was then decanted, and the cells were treated with tianeptine dissolved in growth media and incubated at 37 degrees Celsius for 2 hours. The supernatant was then frozen.

The control cells were incubated in growth media for 2 hours and the LPS control was treated with 1ug/mL of LPS dissolved in growth media and incubated for 2 hours. The concentration of tianeptine used was as follows; 10, 1.25, 0.16 ug/mL for Raw 264.7 cells and 0.156, 0.0195, 0.00244 ug/mL for microglial cells based on dose response curves generated in this study and equivalent dosages between cell lines. Each group was run in triplicate, and each sample was run twice with the ELISA kit to ensure accurate results.

Phagocytosis assay

The phagocytic activity of Raw 264.7 and microglial cells was tested using the Vybrant Phagocytosis Assay Kit (V-6694, Invitrogen) according to the manufacturers protocol. The tianeptine concentrations used were the same as previously described.

Statistical analysis

The data analysis was completed using Prism 10.0 software (Graph Pad, 10.1, San Diego, CA). The assay replicating independence and significance was determined by two-way ANOVA with Bonferroni multiple comparisons, one-way ANOVA, and Student's t-test. Each cell culture experiment was conducted independently at least twice on different days. A P value ≤ 0.05 was considered significant.

Results

- Tianeptine Demonstrates a Higher Cytotoxicity Profile in RAW 264.7 Macrophages Compared to Microglia

A two-hour exposure to varying doses of tianeptine produced a U-shaped cytotoxicity response in both RAW 264.7 macrophages and microglial cells. Notably, mid-range to higher doses (RAW: 0.0781 – 5 µg/mL; Microglia: 0.0781 – 5 µg/mL) led to significantly lower cytotoxicity. These doses correspond to levels seen in therapeutic plasma concentrations based on prior pharmacokinetic studies of tianeptine's respiratory and opioid-related effects [8]. Brain derived microglial cells displayed a robust resistance to cytotoxic effects at equivalent doses than peripheral macrophages. These specific dose ranges were used in subsequent cytokine expression and phagocytosis experiments (Figure 1).

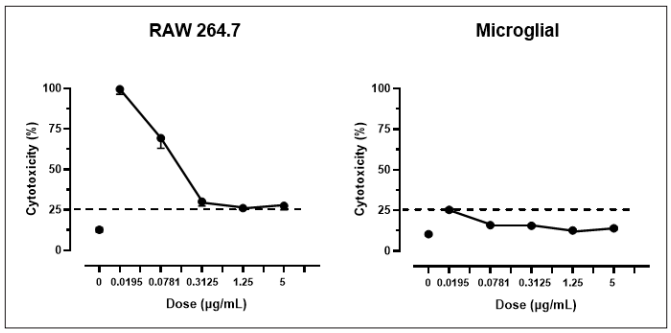

Figure 1: Tianeptine 2-hour cytotoxicity profile in both RAW 264.7 macrophages and microglial cells, with reduced cytotoxicity compared in mid to higher doses. Microglial cells exhibited lower levels of cytotoxicity when compared to peripheral macrophages at equivalent doses of tianeptine. Dashed line represents 25% cytotoxicity in both cell lines.

- Tianeptine Reduces TNF-α Expression in Both Peripheral and Central Macrophages

Following a 2-hour exposure to tianeptine-only conditions, both RAW 264.7 and microglial cells exhibited markedly reduced TNF-α secretion compared to LPS-stimulated controls. The suppression of TNF-α was consistent across both cell types, suggesting a direct anti-inflammatory effect of tianeptine in the absence of a pro-inflammatory stimulus (Figure 2).

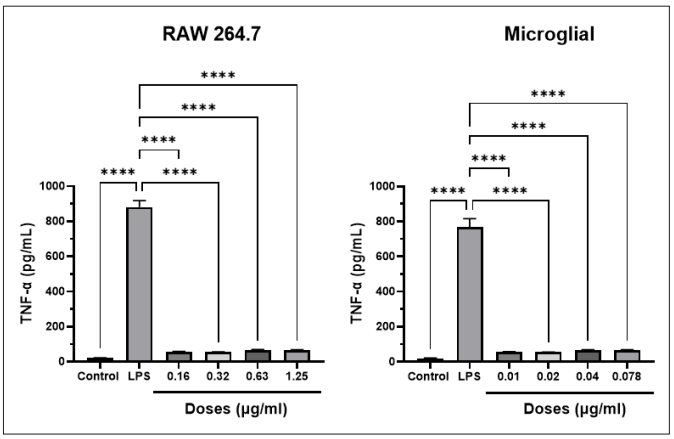

Figure 2: 2-hour exposure of tianeptine significantly suppressed TNF-α secretion in both RAW 264.7 and microglial cells compared to LPS controls. Data are expressed as means ± SEM. Statistically significant results by two-way ANOVA indicated by asterisks **** < 0.0001.

- Tianeptine Increases IL-10 Expression, Particularly in Microglia

In contrast to its suppression of TNF-α, tianeptine significantly increased IL-10 levels in both macrophage types. Microglial cells, however, demonstrated a greater upregulation of IL-10 across all tested doses compared to RAW 264.7 macrophages. A dose-dependent decrease in IL-10 was observed in both cell lines. The dose selection again reflected the equivalent dosage identified in Figure 1, supporting a consistent model for comparing cell-specific immunomodulatory outcomes (Figure 3).

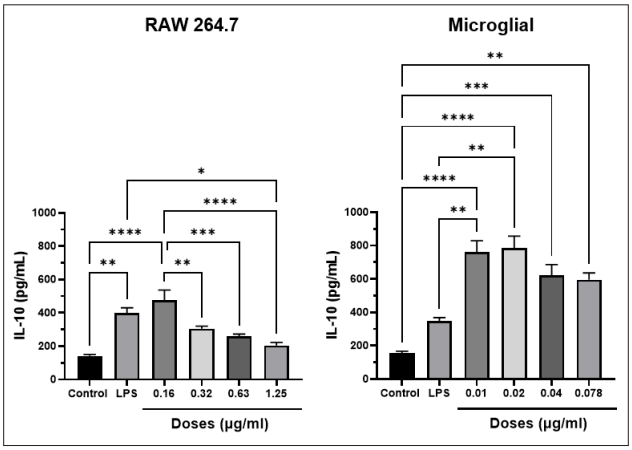

Figure 3: Tianeptine increased IL-10 protein secretion in both RAW 264.7 and microglial cells compared to controls and LPS-controls. Microglial cells demonstrated higher levels of IL-10 expression when compared to peripheral macrophages at equivalent doses. Data are expressed as means ± SEM. Statistically significant results by two-way ANOVA indicated by asterisks * p < 0.05, ** p < 0.01, *** p < 0.001, **** < 0.0001.

- Pre-treatment of tianeptine exacerbates pro-inflammatory cytokine response

Pre-treatment with tianeptine, followed by induction of inflammation using LPS resulted in significant increases in TNF-α secretion compared to untreated controls, except for high dose tianeptine exposure in peripheral macrophages. In parallel, IL-10 expression was reduced in both cell types in a dose-dependent manner. Microglial exhibited a greater relative decrease in IL-10 at equivalent doses of tianeptine, while an increase in TNF-α expression was noted when compared to RAW 264.7 macrophages (Figure 4).

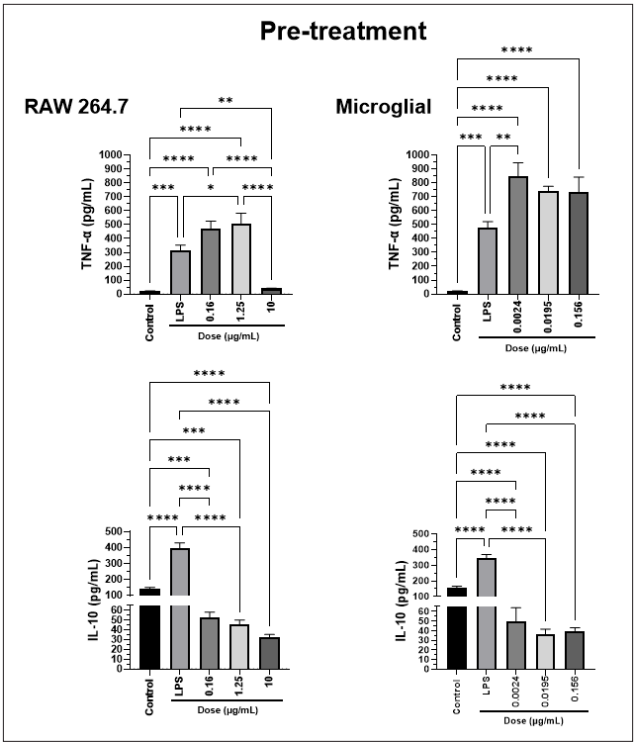

Figure 4: Pre-treatment with tianeptine prior to LPS stimulation increased TNF-α expression and decreased IL-10 expression in both RAW 264.7 and microglial cells compared to LPS-controls. Data are expressed as means ± SEM. Statistically significant results by two-way ANOVA indicated by asterisks * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** < 0.0001.

- Post-treatment of tianeptine decreases pro-inflammatory cytokine response in a dose-dependent manner

After induction of an inflammatory state using LPS stimulation, post treatment with tianeptine reduced TNF-α expression in both RAW 264.7 and microglial cells in a dose-dependent manner when compared to LPS-controls. IL-10 expression remained reduced relative to control and LPS-control levels. Microglial and peripheral macrophage cells exhibited different expressions of TNF-α and IL-10 when exposed to equivalent doses of tianeptine (Figure5).

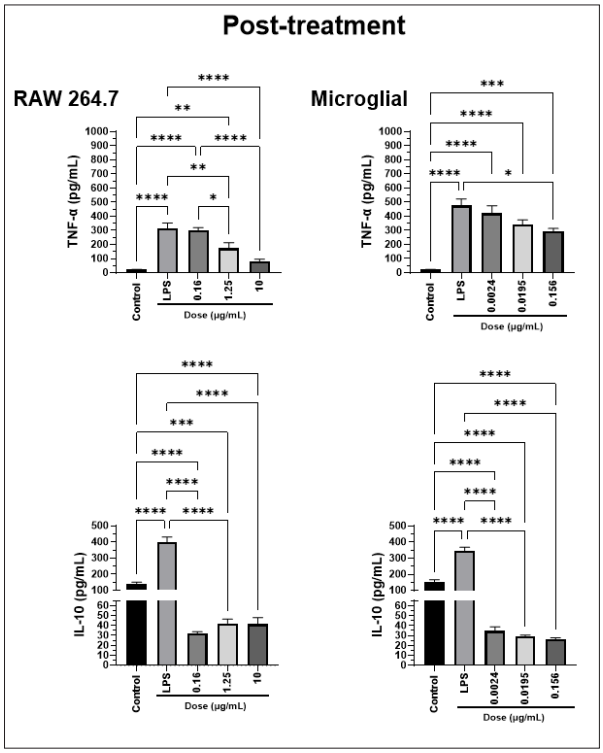

Figure 5: Post treatment with tianeptine after LPS stimulation decreased TNF-α expression in a dose-dependent manner in both RAW 264.7 and microglial cells when compared to LPS-controls. IL-10 expression was reduced compared to both controls and LPS-controls. Data are expressed as means ± SEM. Statistically significant results by two-way ANOVA indicated by asterisks * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** < 0.0001.

- Tianeptine Decreases Phagocytic Activity Except at High Doses in Microglia

Phagocytosis assays revealed that tianeptine significantly suppressed engulfment capabilities in both macrophage types at low to moderate doses. Interestingly, at the 0.156 µg/ml dose tested in microglial cells, restored phagocytic activity was not statistically different compared to control levels, a pattern not seen in RAW 264.7 cells. These results suggest that phagocytic capacity may be dose-sensitive and cell-type-specific under tianeptine exposure (Figure 6).

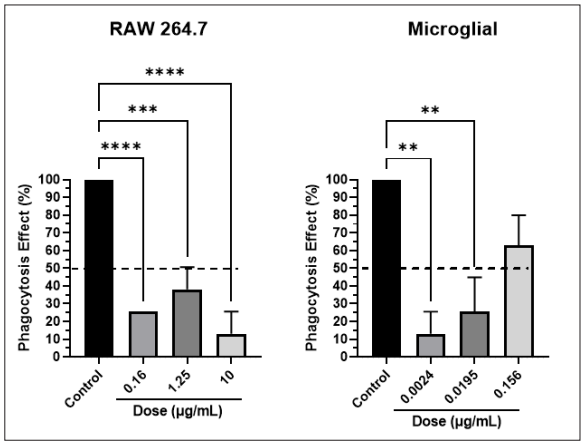

Figure 6: Tianeptine reduced phagocytic activity in both RAW 264.7 and microglial cells at low to moderate doses of tianeptine. Higher doses of tianeptine restored partial recovery of macrophage activity in microglial cells not seen in peripheral macrophages.

Statistically significant results by one-way ANOVA indicated by asterisks ** $p < 0.01$, *** $p < 0.001$, **** < 0.0001.

Discussion

The findings in this study support a direct immunoregulatory role for tianeptine, with prominent anti-inflammatory activity in both peripheral and central immune cells. The U-shaped cytotoxicity curve observed in Figure 1 suggests that, at therapeutically relevant concentrations, tianeptine may actively mitigate inflammation-induced cell death. This effect is consistent with prior reports describing cellular protective effects in inflammatory models [14].

The suppression of TNF-α (Figure 2) and concurrent upregulation of IL-10 (Figure 3) across both macrophage types further strengthens the hypothesis that tianeptine shifts immune activity toward an anti-inflammatory state. This pattern of cytokine expression aligns with literature demonstrating tianeptine's ability to suppress pro-inflammatory responses in both CNS and peripheral tissues [12,13]. The stronger IL-10 induction in microglia may reflect differential receptor expression, particularly of μ-opioid receptors, which are more densely expressed in CNS-associated immune cells [15]. These receptors have been implicated in modulating inflammation via IL-10-linked signaling pathways [15].

Pre-treatment with tianeptine prior to induction of an inflammatory state led to an exacerbation of pro-inflammatory cell markers, mainly the increased expression of TNF-α, when compared to controls (Figure 4). This suggests that tianeptine has a diminished role in prophylactic prevention of an inflammatory state, rather, it acts as a primer for macrophages toward heightened immune responsiveness when administered prior to an inflammatory insult. In contrast, post-treatment with tianeptine following LPS exposure led to a dose-dependent attenuation of TNF-α release compared to LPS only controls (Figure 5), demonstrating clear anti-inflammatory properties of tianeptine when exposed to an already established inflammatory state [13]. Notably, IL-10 expression was relatively similar when compared between pre and post treatment trials, suggesting that, in the context of existing inflammation, tianeptine may act through alternative anti-inflammatory pathways.

The findings in the current study provide insight into the temporal effects of tianeptine and how timing of exposure to tianeptine influences whether inflammatory signaling is attenuated or amplified. Based on these data, tianeptine is more effective in mitigating existing inflammatory states than it is in blocking their initiation [12]. The lack of responsiveness to tianeptine regarding IL-10 levels in the context of an existing inflammatory state (Figure 5), warrants further research that should be aimed at identifying anti-inflammatory pathways/cytokines effected by tianeptine in an existing inflammatory state, such as IL-6 or TGF-β [16].

The phagocytosis data during the study (Figure 6) can also shed light on tianeptine's immunomodulatory effects. Reduced phagocytic capacity is consistent with an anti-inflammatory state, as active phagocytosis often coincides with M1-type inflammatory activation. However, the restoration of phagocytosis to near control levels at higher tianeptine doses in microglia could represent a rebalancing toward an M2 anti-inflammatory phenotype – a hypothesis supported by similar findings in other neuroimmune models [13].

The importance of the difference in cytokine expression in peripheral and central macrophages cannot be understated, as these findings point to potential mechanisms specific to each cell type. RAW 264.7 cells, peripheral macrophages, demonstrated a more muted response to tianeptine, when compared to microglia, in most of the experiments performed in this study. This may be due to differences in receptor expression and signaling pathways between central and peripheral immune cells. For instance, microglia have been found to express much higher levels of pattern recognition receptors and μ-opioid receptors, which may play a role in enhancing the sensitivity to tianeptine's immunomodulatory effects [11,15,17,18]. In contrast, peripheral macrophages rely much more heavily on classical pro-inflammatory pathways, which may limit their responsiveness to tianeptine mediated anti-inflammatory signaling [19].

The findings of this study are most appropriately interpreted as an advancement in the insight into neuroimmune modulation rather than support for therapeutic relevance. Although tianeptine attenuated inflammatory cellular responses, particularly involving central immune cells, these effects are not confirmed to demonstrate any clinical benefit. Tianeptine has been evaluated across many psychiatric and inflammatory conditions including major depressive disorder, depression with comorbid alcohol use disorder, bipolar disorder, posttraumatic stress disorder, and irritable bowel syndrome. In these trials, there was no evidence that treatment with tianeptine was superior to any of the current comparator treatments [20-27]. The findings of these studies, along with results from this experiment, infer that, although tianeptine demonstrated immunomodulatory properties, those effects do not confer meaningful clinical relevancy. Furthermore, while inflammatory processes are frequently observed in depression and other stress-related psychiatric disorders [28,9,10], the presence of this phenomenon does not imply that pharmacological attenuation of inflammation will yield antidepressant effects.

In this context, the data presents neurobiological insight into immunomodulatory actions, potentially influenced by μ-opioid receptor engagement, without extending claims of clinical relevance, particularly considering tianeptine's established safety liabilities, including respiratory depression and abuse potential [29], as well as its limited regulatory feasibility.

The findings demonstrated in this study are largely in agreement with Castanon et al. (2004) and Ślusarczyk et al. (2018), who observed tianeptine-mediated reductions in pro-inflammatory cytokines and microglial M1 polarization. However, phagocytic suppression contrasts with reports of enhanced cellular repair under tianeptine treatment, indicating potential dose and/or context-dependent immunomodulatory effects that warrant further exploration [12,13,30].

Conclusions

This study demonstrates that tianeptine exerts distinct immunomodulatory effects on both central and peripheral immune cells. At therapeutically relevant concentrations, sole exposure to tianeptine reduced cytotoxicity and promoted an anti-inflammatory state by suppressing TNF-α expression and enhancing IL-10 expression. It is important to note that distinct effects were seen in both cell lines used in the current study. CNS resident microglia exhibited a stronger anti-inflammatory response to tianeptine with partial restoration of phagocytic activity at higher doses. These findings provide a mechanistic insight into how tianeptine can modulate immune signaling within neuroinflammatory environments, particularly in resident cells in the CNS. Therapeutic implications should not be inferred from the present data, as prior clinical investigations have failed to demonstrate meaningful

efficacy across psychiatric and inflammatory conditions [20-27].

This study reinforces prior evidence suggesting that tianeptine reduces proinflammatory cytokine expression by enhancing anti-inflammatory signaling [12,13]. However, the observed suppression of phagocytosis, as well as decreased inflammatory expression seen in post treatment trials, point to a potential impairment of host immune defenses [15,31]. Given tianeptine's increasing, unregulated use in the United States [5,32], these findings have broader public health implications by highlighting potential immunological consequences when exposed to tianeptine. Its abuse potential, opioid agonism, and possible impact on host immunity warrant careful regulation and further investigation.

Future research should aim to clarify the receptor specific mechanisms of tianeptine's immunomodulatory effect including the contributory factor of μ-opioid receptor signaling, and immunological consequences that may be relevant to the safety of tianeptine. Ultimately, this work adds more context to the expanding field of research investigating the immunological effects of psychiatric medications [33,34].

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Conflict of Interest
The authors declare no conflict of interest.

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