Review

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Glutathione Depletion in Major Depressive Disorder and Its Impact on Tuberculosis Immunity

Marriam Anjum[1], Mariam Habbak[1], Farah Mawlawi[1], Aemen Siddiqui[1], Vishwanath Venketaraman[1,*]

[1]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA 91766, USA

*Correspondence: vvenketaraman@westernu.edu (Vishwanath Venketaraman)

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Major depressive disorder (MDD) is associated with various biochemical changes that contribute to chronic inflammation and the buildup of reactive oxygen species (ROS) in the body. One of the key alterations observed in MDD is the depletion of glutathione (GSH). This decrease in GSH results from impaired cysteine uptake, reduced glutathione peroxidase (GPx) activity, and mitochondrial dysfunction. In the human body, GSH is a vital intracellular antioxidant responsible for metabolizing ROS and modulating immune responses. This paper summarizes current literature on how GSH depletion associated with MDD disrupts key immunoregulatory functions, specifically as it applies to the immune response to *Mycobacterium tuberculosis* (*M. tb*). Research has shown that this disruption leads to increased oxidative stress and a weakened host immune response. Effective control of *M. tb* depends on balanced ROS activity and GSH-dependent macrophage function. Reduced GSH compromises these processes by limiting the ability of immune cells to function normally. Therefore, individuals with MDD-associated GSH depletion are at risk of developing severe tuberculosis (TB). Understanding this connection has important clinical and public health implications, particularly in regions where TB is endemic and depression is underdiagnosed. Integrating mental health assessment and considering antioxidant supportive strategies may improve TB management, especially in high-burden settings. Emerging evidence suggests that increasing levels of GSH through adjunct treatment with N-acetylcysteine or liposomal GSH may improve both depressive symptoms and the antimicrobial immune response. Despite this supporting research, further exploration is needed to clarify their therapeutic potential in individuals with comorbid MDD and TB.

Keywords: glutathione; major depressive disorder; tuberculosis; reactive oxygen species; immune system

Introduction

Major Depressive Disorder (MDD) is a psychiatric condition characterized by many symptoms, including persistent low mood, lack of energy, and anhedonia [1]. According to the World Health Organization, approximately 5% of adults are affected by depression at some point in their lives [2]. MDD is diagnosed when at least five characteristic symptoms are present over a two-week period. Beyond its clinical diagnosis, the manifestation of depression on a cellular level is associated with various altered biochemical pathways.

Inflammation and oxidative stress play a central role in the pathophysiology of depression [3]. Metabolomic studies have shown altered amino acid metabolism in individuals with MDD, including decreased plasma cystine levels. This reflects the reduced availability of cysteine, the rate-limiting precursor for glutathione (GSH) synthesis [4]. In addition, impaired glutathione peroxidase (GPx) activity and mitochondrial dysfunction further contribute to decreased intracellular GSH levels [5,6]. Because GSH is a key regulator of redox balance and immune function, its depletion may weaken host defenses and increase vulnerability to infections.

GSH is a potent intracellular antioxidant composed of the amino acids glutamine, cysteine, and glycine. In its reduced form, GSH plays a critical role in modulating inflammatory responses and metabolizing reactive oxygen species (ROS) in the body to protect cells from oxidative damage.

Biosynthesis of GSH occurs intracellularly in a series of two steps predominantly in the liver (Fig. 1). In the first step, glutamate cysteine ligase (GCL) catalyzes the formation of γ-glutamylcysteine from cysteine and glutamate. An amide bond is formed between the carboxyl group of glutamate and the amino group of cysteine. In the next step, glutathione synthetase adds glycine to the dipeptide in an ATP-dependent reaction to produce γ-glutamyl cysteine glycine. Once synthesized, GSH can be transported out of the hepatocytes into the plasma to have systemic effects [7,8].

The antioxidant activity of GSH is largely attributed to the sulfhydryl group (-SH) on the cysteine residue [7]. This highly reactive group donates electrons to neutralize free

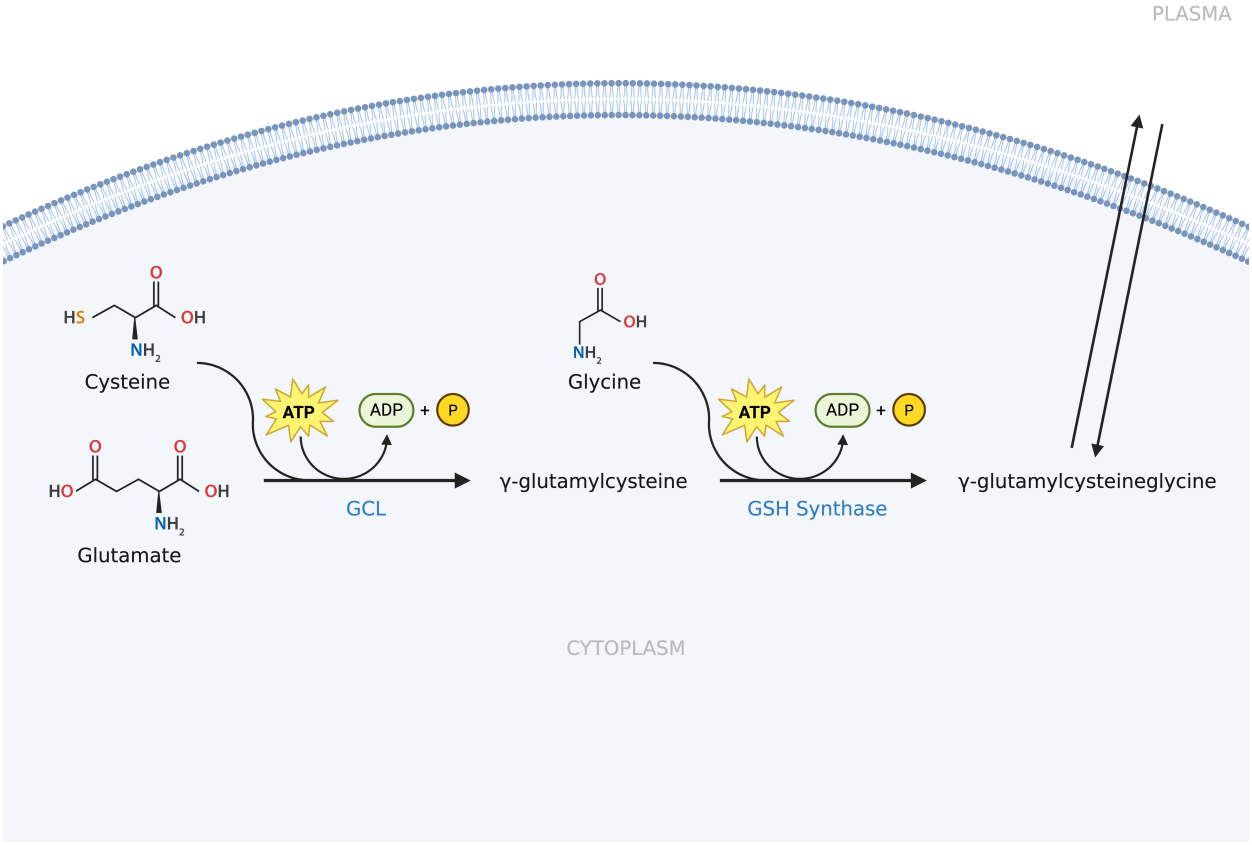

Fig. 1. Biosynthesis of Glutathione (GSH). This figure depicts the intracellular biosynthesis of GSH. This illustration was created using BioRender (https://www.biorender.com/).

radicals and supports redox reactions that maintain cellular stability. Additionally, the sulfhydryl group enables conjugation reactions to make harmful compounds more water-soluble and easier to excrete from the body. The properties of sulfur also allow it to form disulfide bonds with proteins to regulate protein function. Through these mechanisms, GSH modulates inflammatory responses by regulating immune cell reactivity and suppressing pro-inflammatory cytokine production [9].

Mycobacterium tuberculosis (*M. tb*) is a chronic infectious disease that primarily affects the lungs. The pathogen is transmitted by airborne droplets and persists within host macrophages. Control of *M. tb* relies on the host cellular immunity, particularly the activation of macrophages and T cells. Oxidative stress and the availability of antioxidants like GSH are important modulators of the host immune defense against this intracellular pathogen.

In this paper, we will discuss how GSH depletion associated with MDD disrupts these key immunoregulatory functions, specifically as it applies to the immune response to TB. We propose that glutathione depletion in MDD disrupts mitochondrial energy production and redox balance. This alteration impairs macrophage activity and weakens the Th1-mediated immune response against *M. tb*. Together, these findings suggest a shared mitochondrial and immunometabolic pathway linking depression and susceptibility to infectious disease.

Methods

A comprehensive literature review was conducted to explore the interrelationships between depression, tuberculosis (TB), and oxidative stress. Searches were performed across electronic databases such as PubMed and Google Scholar, using terms such as “depression”, “tuberculosis”, “oxidative stress”, “Glutathione”, “GSH”, “mycobacterium”, “psychiatric disorders”, “mental health”, and “antioxidants”. The review included observational and experimental studies published between January 2000 and December 2025 that focused on the connections between these conditions. Studies were selected based on their relevance, study design, language (English), and empirical data quality. Others were excluded due to their lack of relevance, limited research support, or publication dates before 1994. Data extraction involved identifying key study details such as design, population characteristics, variables, and findings. This narrative review aimed to summarize current knowledge, assess evidence strength, and suggest future research directions.

Discussion

Mechanisms of Glutathione Depletion in MDD

GSH depletion is a significant biochemical alteration observed in MDD. This results from reduced availability of cysteine, lower activity of GPx, and mitochondrial dysfunction. Understanding these pathways is essential for appreciating how depression creates biological vulnerability to infectious diseases such as TB.

Impaired Cysteine Uptake and GSH Synthesis

Cysteine is the rate-limiting substrate for GSH synthesis. Within neurons, cysteine uptake is primarily mediated by sodium-dependent excitatory amino acid transporters (EAATs), such as excitatory amino acid carrier 1 (EAAC1) [10]. Increased oxidative stress observed in MDD impairs the function of EAAC1 by interfering with its trafficking to the neuronal membrane. This leads to reduced cysteine uptake, which subsequently decreases GSH production [11].

Reduced Glutathione Peroxidase Activity

GPx is a crucial antioxidant enzyme that uses GSH to neutralize ROS. It is critical in maintaining the redox balance within cells and its activity is tightly regulated by the availability of GSH. A study has shown that in MDD, GPx1 expression in oligodendrocytes is reduced [3]. This deficiency results in the buildup of oxidative stress, which contributes to cellular damage and neuroinflammation.

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction plays a key role in oxidative imbalance seen in MDD [12]. Mitochondria are responsible for creating ATP for cells via oxidative phosphorylation. During this process, electrons are transferred through various complexes and ultimately reduce oxygen to water at complex IV. Normally, a small amount of electrons can leak from the electron transport chain (ETC) and react with oxygen to form superoxide anion. In healthy cells, these ROS are neutralized by antioxidant enzymes such as GSH. However, in MDD, mitochondria have reduced efficacy, and the ETC becomes inefficient [13]. The impaired process leads to increased electron leakage and, therefore, increases superoxide formation beyond normal levels.

Beyond ROS accumulation, additional indicators characterize mitochondrial dysfunction in MDD. Mitochondrial membrane potential ($\Delta\Psi m$) reflects the ability of the ETC to maintain the proton gradient across the inner mitochondrial membrane that drives ATP synthesis. A reduction in $\Delta\Psi m$ reflects impaired respiratory efficiency and early bioenergetic dysfunction. Depolarization of the mitochondrial membrane has been associated with impaired cellular metabolism and increased oxidative stress, which further characterizes mitochondrial dysfunction in MDD [14]. A study using induced neural progenitor cells from MDD patients has demonstrated reduced maximal respiration rates and less hyperpolarized (more depolarized) membrane potentials, confirming that membrane depolarization is a functional consequence of mitochondrial impairment in depression [15].

Structural alterations in mitochondrial content also contribute to cellular dysfunction in MDD. Mitochondrial mass represents the total mitochondrial content within a cell and reflects the balance between mitochondrial biogenesis and mitophagy, the selective removal of damaged mitochondria through autophagic degradation. Disruption of this balance can reduce mitochondrial capacity or allow accumulation of dysfunctional organelles, both of which impair ATP production and redox regulation [16–19]. Therefore, assessment of mitochondrial mass alongside $\Delta\Psi m$ and ROS levels provides a more comprehensive evaluation of mitochondrial instability in MDD.

In a research study that was performed using Seahorse assays, fibroblast cells from individuals with MDD showed reduced mitochondrial respiration. The parameters measured included decreased basal respiration, ATP-linked respiration, and maximal respiration. This directly demonstrates the functional compromise of the ETC and oxidative phosphorylation in MDD [20]. In another study performed, peripheral blood cells from MDD patients exhibited decreased oxygen consumption rates in seahorse assays [21]. T cells obtained from patients with MDD also exhibited reduced respiratory and glycolytic capacity. Both of these studies support that there is reduced mitochondrial respiration in patients with MDD.

Immune Consequences of GSH Depletion

GSH also plays a direct role in immune regulation. In addition to GSH neutralizing oxidative stress, it regulates the immune system by controlling immune cell activity and reducing the release of proinflammatory cytokines. Low GSH levels in MDD promote a chronic pro-inflammatory state, which leads to the progression of depressive symptoms. This ongoing inflammation also increases oxidative stress, creating a cycle that can worsen MDD.

Together, these findings suggest that MDD is associated not only with increased oxidative stress but also with impaired mitochondrial energy production that extends beyond the central nervous system. Because immune cells rely on intact mitochondrial function to generate energy and regulate antimicrobial responses, bioenergetic impairment could weaken the body's ability to control infections such as TB.

Pathogenesis of M. tb and the Role of GSH in Host Defense

Having established how MDD depletes GSH and impairs cell function, we now examine how these processes are essential for controlling *M. tb* infection.

M. tb Infection and Immune Evasion

M. tb is a slow-growing intracellular pathogen that primarily affects the lungs but can disseminate to other organs in the body. Infection occurs through the inhalation of airborne droplets containing the bacteria, which are engulfed by alveolar macrophages. *M. tb* evades immune destruction by inhibiting phagosome-lysosome fusion and resisting intracellular killing mechanisms, allowing it to replicate within host cells [22].

The host immune response to *M. tb* involves both the innate and adaptive immune system. Cells such as macrophages, dendritic cells, and natural killer cells recognize pathogen-associated molecular patterns via pattern recognition receptors. This recognition activates inflammatory signaling pathways and leads to the release of cytokines that help recruit and activate additional immune cells [23].

Granuloma Formation and Th1 Immunity

A hallmark of the immune response to *M. tb* is the formation of granulomas, organized clusters of macrophages, T cells and other immune cells that contain the infection (Fig. 2). T-helper-1 (Th1) subset of CD4+ T cells plays a central role by secreting interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) to activate macrophages and enhance their bactericidal activity [24].

ROS-Mediated Bacterial Killing and the Critical Role of GSH

A key mechanism by which activated phagocytes inhibit the growth of *M. tb* is through the generation of ROS and reactive nitrogen species (RNS). This respiratory burst process occurs in mononuclear and polynuclear phagocytes. It results in the rapid production of superoxide via NADPH oxidase. Superoxide (O_2^-) can then be converted into hydrogen peroxide (H_2O_2), hypochlorite (HClO), hydroxyl radicals (OH·), and peroxynitrite ($ONOO^-$). These ROS cause damage to microbial DNA, lipids, proteins, and sensitive cellular components like iron-sulfur cluster proteins. Nitric oxide (NO) is a key ROS in the anti-TB response. While *M. tb* can tolerate low levels of ROS by activating DNA repair mechanisms, high ROS concentrations are lethal to the bacteria [25]. This highlights that effective TB control depends not on excessive oxidative stress, but on tightly regulated redox balance. Macrophages rely on intracellular antioxidants such as GSH to regulate oxidative killing mechanisms while protecting themselves from oxidative damage [26,27].

A study has shown that GSH levels correlate with the immune competence in individuals exposed to *M. tb*, highlighting its role as a modulator of the host-pathogen interaction [28].

In a study done in murine models, pharmacologically induced GSH depletion has been shown to increase *M. tb* burden and impair granuloma formation in extrapulmonary tissues. This is associated with disrupted cytokine release and impaired immune coordination [29].

Therefore, sufficient GSH is essential not only for protecting immune cells but also for enhancing antimicrobial activity against *M. tb*.

Role of Regulatory T Cells and Platelets in TB and MDD

The immune response to *M. tb* involves additional regulatory mechanisms that are dysregulated in MDD, further strengthening the biological connections between these conditions.

T_{reg} Cells in TB Immunity

Granulomas are also enriched with CD4+ regulatory T (T_{reg}) cells and effector T (T_{eff}) cells [30]. T_{reg} cells have a phase-dependent role in the immune response to tuberculosis infection. In the acute phase, specifically the first two weeks of infection, low levels of T_{reg} cells decrease bacterial burden and therefore help contain the infection. In the chronic phase, higher levels of T_{reg} cells are needed to regulate the immune response and prevent excessive inflammation. In studies on mice and non-human primates, TB-resistant subjects were found to have higher T_{reg} cell frequencies. Macaques that developed latent TB had higher baseline pre-infection T_{reg} cell frequencies compared to animals that developed active disease, highlighting the importance of T_{reg} cells in preventing disease progression. In human studies, bronchoalveolar lavage was used to measure frequencies of T_{reg} cells at the site of infection of pulmonary TB subjects. T_{reg} cell frequencies were higher at the site of infection compared to in the peripheral blood [31].

Qualitative studies on T_{reg} cell function have revealed that the role of T_{reg} cells in chronic TB disease is compromised by T_{eff} cells that are resistant to T_{reg} cell-mediated suppression. This is thought to arise from TB infection driving the expansion of activated human leukocyte antigen D-related (HLA-DR)+ CD4+ T cells. Anti-tubercular treatment reduces the frequency of HLA-DR+ cells, restoring T_{eff} cell sensitivity to T_{reg} cell-mediated suppression [31].

Platelet-Mediated Immune Modulation

Platelets also modulate TB immunity. Beyond their role in hemostasis, platelets have important pro-inflammatory and anti-inflammatory properties [32]. A high platelet to lymphocyte ratio has been observed in human subjects with active TB due to both increased absolute platelet counts and decreased absolute lymphocyte counts compared to healthy subjects, subjects with latent TB, and those with cured TB [33]. While platelets were found to drive inflammation and tissue degradation [34], they also enhance the killing of intracellular *M. tb* [33].

Immunohistochemical analysis on lymph nodes and lung specimens of subjects with active TB revealed platelet

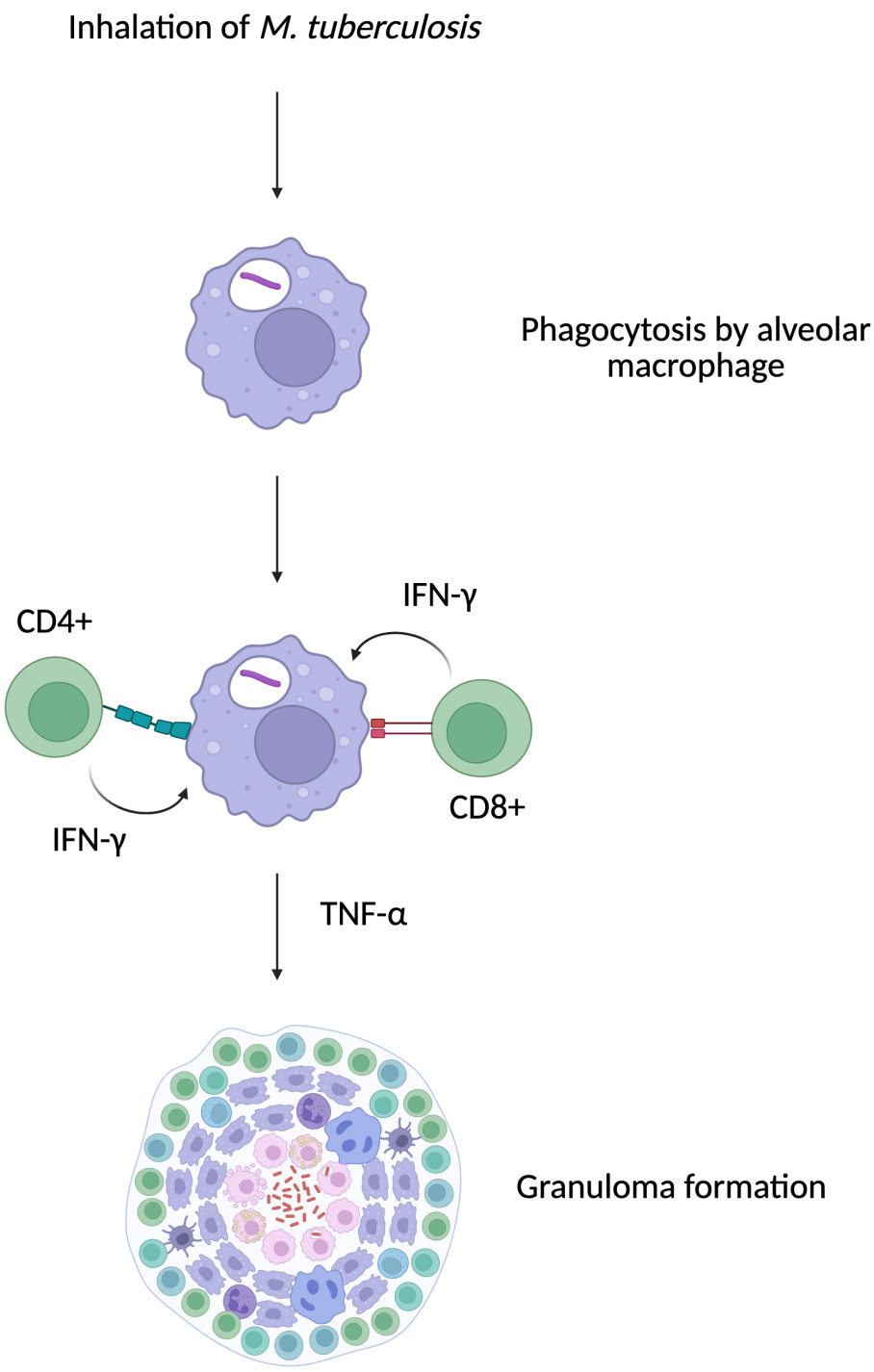

Fig. 2. Immune response to *Mycobacterium tuberculosis* (*M. Tb*) and granuloma formation. This figure shows the key cells involved in the immune system response to *M. tb* and granuloma formation. This illustration was created using BioRender (https://www.biorender.com/).

clusters surrounding granulomas with colocalization of platelets with macrophages and lymphocytes. Many platelet-associated genes were found to be upregulated in pulmonary TB granulomas compared to normal lung tissue. Activated platelets affect the response of T cells and macrophages to *M. tb* through the release of soluble factors, including transforming growth factor-beta (TGF-β) and platelet factor 4 (PF4), also known as CXC chemokine ligand 4 (CXCL4) [33].

TGF-β: A Critical Link Between Platelets, GSH, and Immune Suppression

TGF-β downregulates GSH [35] and suppresses T cells in granulomas. This results in increased ROS, restricted IFN-γ release, decreased survival, proliferation, and differentiation of effector T cells, and increased bacterial burden [36]. PF4 prevents monocyte apoptosis, promotes differentiation of monocytes into M4-polarized macrophages, and induces phagocytosis and generation of ROS [34,37].

Collectively, these immune mechanisms demonstrate that successful containment of *M. tb* requires coordinated redox regulation, mitochondrial integrity, and balanced cytokine signaling. These processes are compromised in the setting of glutathione depletion, which occurs in MDD and TB.

These same platelet-mediated mechanisms operate in MDD, where there are increased levels of activated platelets [38]. Depressed patients exhibit morphological and functional platelet changes consistent with a hyperreactive state, with increased levels of activated platelets secreting TGF-β [39]. TGF-β levels in MDD show varied patterns. While some studies have shown positive correlations between MDD and TGF-β levels, specifically in subpopulations such as those with childhood maltreatment, others have shown decreased levels of TGF-β in patients with MDD compared to healthy patients [40]. Despite these various findings, its role as an immune regulatory cytokine in depression is well established, as we discussed earlier.

TGF-β is essential for inducing FoxP3 expression in naive T cells and promoting T_{reg} cell differentiation [41]. However, despite elevated platelet-derived TGF-β, MDD patients exhibit decreased CD4+CD25+FoxP3+ T_{reg} proportions that correlate with depression severity [42,43]. This T_{reg} cell deficiency can reflect dysregulated TGF-β signaling in depression. By inhibiting GSH synthesis, TGF-β is a potential mechanistic link between platelet activation, TGF-β secretion, and GSH depletion in MDD [44,45]. This connection represents an additional pathway through which the immune dysregulation in depression contributes to impaired defenses, given the critical role of T_{reg} cells in controlling TB progression.

PI3K-Akt-mTOR Dysregulation in MDD and TB

In addition to GSH depletion and platelet-mediated immune modulation, the pathogenesis of MDD and TB involves shared disruption of a common immune signaling pathway.

The PI3K-Akt-mTOR Pathway

The phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K-Akt-mTOR) signaling pathway plays a central role in regulating T_{reg} cells as well as cellular survival and metabolism [46,47].

PI3K is a lipid kinase that responds to extracellular stimuli and produces a secondary messenger to initiate downstream signaling. Akt, also known as protein kinase B, is a serine-threonine kinase that promotes cell survival, metabolism, and growth once activated [48]. mTOR is another serine-threonine kinase that forms complexes such as mTORC1 and mTORC2 to regulate various cellular processes, including autophagy and protein synthesis [49].

PI3K-Akt-mTOR Pathway Suppression in TB

As discussed earlier, T_{reg} cells are a specialized subset of CD4+ T cells that help control and suppress excess immune response. FoxP3 is a transcription factor expressed by some T_{reg} cells, which controls their development and function. This transcription factor is crucial for T_{reg} function to decrease the immune response [48,50].

In a study comparing blood from healthy individuals and those with active TB, researchers found that FoxP3+ T_{reg} cells were significantly increased in TB patients [46]. Additionally, components of the PI3K-Akt-mTOR pathway, including phosphorylated Akt and mTOR, were decreased in T cells of TB patients. When the signaling pathway function is decreased, T cells are more likely to adopt a FoxP3+ T_{reg} cell phenotype instead of differentiating into inflammatory effector cells. This pathway suppression in TB likely contributes to the expansion of T_{reg} cells observed in patients [51]. These findings indicate that the PI3K-Akt-mTOR pathway is decreased in TB patients, which helps explain the observed increase in FoxP3+ T_{reg} cells. As a result, this could decrease the host's ability to clear *M. tb.*

PI3K-Akt-mTOR Pathway Suppression in MDD

Similar alterations occur in MDD, where this pathway is critical for regulating synaptic protein synthesis and neuronal survival [52]. In a study analyzing postmortem brain tissue from individuals diagnosed with MDD, it was found that there was decreased mTOR signaling activity, including decreased phosphorylation of mTOR and its downstream targets such as p70S6K and eIF4b. These deficits contribute to the structural and functional changes in the brain [53]. For example, reduced mTOR signaling has been associated with lower synaptic protein expression and impaired translation initiation. This is thought to underlie weakened synaptic connectivity in key mood-regulating regions of the brain, including the prefrontal cortex and hippocampus [53].

Animal models of chronic stress and depressive-like behavior also demonstrate reduced phosphorylation of Akt and downstream mTOR targets. This supports that depression is linked to the downregulation of PI3K-Akt-mTOR signaling in neural circuits involved in emotion and reward [54]. These findings parallel what is observed in TB, where suppressed mTOR activity contributes to altered immune cell behavior.

In the same study, the connection between mTOR dysfunction and depression is also supported by research on rapid-acting antidepressants such as ketamine, which can activate the PI3K-Akt-mTOR pathway [54]. This highlights the therapeutic relevance of restoring PT3K-Akt-mTOR pathway activity to improve symptoms of both MDD and TB.

Epidemiological and Biological Integration of TB and MDD

The preceding sections have established that TB and MDD share many mechanisms, including GSH depletion, mitochondrial dysfunction, platelet-mediated immune dysregulation, and the PI3K-Akt-mTOR pathway suppression. The similarities explain how MDD and TB work synergistically through biological, social and behavioral mechanisms to magnify disease burden [55].

Bidirectional Relationship

TB can cause depression through cytokine dysregulation mechanisms and psychosocial stressors such as stigma, isolation and chronic illness burden. Conversely, depression increases TB risk through immune suppression, poverty, and malnutrition. Individuals with these factors may experience worsened treatment outcomes due to medication non-adherence and increased disease duration. The bidirectional relationship is supported by epidemiological evidence showing that depression increases TB risk with hazard ratios ranging from 1.15–2.63, while TB patients experience depression prevalence rates of 23–48%, which is significantly higher than 6.8% observed in general populations [56,57].

MDD Compromises the Immune Response to Tuberculosis

One of the key immunological consequences of MDD is GSH depletion. As previously discussed, GSH is a major intracellular antioxidant essential for maintaining redox homeostasis and regulating immune responses. In individuals with MDD, reduced availability of cysteine, decreased GPx activity, and mitochondrial dysfunction lead to lower intracellular GSH levels [5]. This deficit limits the ability of immune cells to mount an effective response to intracellular pathogens such as *M. tb*.

GSH depletion also affects the production of key cytokines such as IFN-γ, which is crucial for macrophage activation and the coordination of a Th1 immune response [37]. Additionally, mitochondrial dysfunction in MDD contributes to reduced ATP production and ROS generation, further impairing immune responses. As a result of impaired immune surveillance and pathogen control, individuals with MDD are more susceptible to TB [58].

Chronic low-grade inflammation is a well-established feature of MDD, often marked by elevated levels of interleukin-6 and TNF-α, and C-reactive protein [59]. Over time, this can cause immune exhaustion, where there is decreased immune system responsiveness to pathogens. In the case of *M. tb*, where a coordinated immune response is crucial to control the infection, this inflammatory state promoted by MDD may increase susceptibility to TB [60]. In another study, it was found that interleukin-1R2 mediates depressive symptoms in TB patients through specific inhibition of interleukin-1 inflammatory signaling. This finding indicates a shared pathophysiological mechanism between both conditions [61]. Ultimately, this supports that individuals with MDD may be at an increased risk for *M. tb* infection.

GSH depletion appears to be a critical link between MDD and the impaired immune control of *M. tb*. These insights discussed above raise important clinical implications, especially in regions where TB is endemic and mental health disorders are underdiagnosed or undertreated, as evidenced by literature showing that mental health comorbidities in TB patients are frequently unrecognized and poorly managed in TB-endemic settings [62].

Epidemiological Evidence

The relationship between depression and increased severity of TB is recognized as a significant public health concern. A nationwide study in Korea revealed that individuals with depression had a 2.63 times greater risk of developing TB. Notably, the study revealed a dose-response relationship between the two conditions, indicating that patients with more severe depression were at an even higher risk of contracting TB compared to those with milder depression [58]. Similarly, a large-scale study in Taiwan involving 34,765 individuals with depression and 138,187 without it found that those with depression had a significantly higher incidence of pulmonary TBs in addition to other infections. The analysis revealed that depression significantly elevated the risk of developing a more severe pulmonary TB [63].

Clinical and Public Health Implications

The comorbidity of MDD and TB presents significant clinical and public health challenges. Depression not only increases susceptibility to developing severe TB but also complicates its management. Individuals with both conditions are more likely to exhibit poor health-seeking behaviors and non-adherence to treatment regimens, leading to worse outcomes such as increased morbidity, mortality, drug resistance, and sustained disease transmission. One study specifically also showed that in elderly individuals with tuberculosis, depressive episodes were associated with functional impairment in nearly 40% of patients, and suicidal ideation in 20%. Depressive episodes were shown to lead to poorer treatment outcomes, with treatment success rates dropping from 79.1% to 64.7% [64]. A study examining primary-care patients initiating antidepressant treatment found that depression significantly impacted functional status and disability, which was assessed over several months.

These findings highlight the importance of addressing mental health to improve treatment adherence and outcomes in TB patients [65].

Furthermore, anti-TB drugs such as isoniazid and cycloserine are known to induce or exacerbate psychiatric symptoms, including depression and anxiety [66]. Mental health comorbidities in TB patients are frequently unrecognized and poorly managed, particularly in TB-endemic settings where mental health infrastructure is limited [67]. The prevalence of depression among individuals with TB is reported to be more than three times higher than in healthy populations [68]. Some researchers suggest that *M. tb* infection may significantly increase the risk of progressing to active disease in individuals with mental illness, particularly when compounded by factors like poor nutrition and overcrowded living conditions. These socio-environmental stressors, combined with the physiological impacts of mental illness, can weaken immune defenses. This creates an environment where *M. tb* infection is more likely to cause active disease [69]. Screening for depressive symptoms in TB-endemic settings may therefore represent not only a mental health intervention, but also an immunological risk stratification strategy. Incorporating redox biomarkers such as intracellular GSH levels into studies of high-risk populations could further optimize this approach and help identify individuals who may be more vulnerable to disease progression.

Therapeutic Potential of GSH Supplementation

GSH supplementation may provide therapeutic benefits in both MDD and TB by reducing oxidative stress and enhancing immune function.

GSH Restoration in Depression

Although direct evidence of GSH supplementation for depression remains limited, multiple studies have shown that N-acetylcysteine (NAC), a precursor to GSH, improves the severity of depressive symptoms. One clinical trial showed that adjunctive NAC treatment resulted in a significant improvement on the Montgomery Asberg Depression Rating Scale (MADRS) in bipolar patients with depressive symptoms [70]. In addition, a meta-analysis of five studies also showed that NAC improved depressive symptoms with good tolerability as measured by significant improvements in MADRS and functionality with NAC compared to placebo [71]. These findings suggest that increasing GSH availability may help mitigate depression through the reduction of oxidative stress.

GSH Restoration in TB

TB progression is also closely linked to oxidative stress and impaired immune regulation. *M. tb* exploits weakened immune systems and oxidative stress environments to progress latent tuberculosis infection (LTBI) to active TB. One study in HIV infected individuals showed that liposomal GSH (L-GSH or Readisorb) supplementation enhanced the TH1 response, which is important for mediating effective immune responses against intracellular pathogens such as *M. tb*. It was also shown to decrease the levels of free radicals and immunosuppressive cytokines, which further limited *M. tb* proliferation [72]. In addition, researchers found that L-GSH supplementation in treated mice caused a significant reduction in *M. tb* burden in the lungs, decreased oxidative stress, and increased the production of IFN-γ, TNF-α, IL-17, IL-10, and TGF-β1. When combined with Rifampin, L-GSH supplementation achieved better control of *M. tb* infection in the lungs and significantly reduced the levels of oxidative stress compared to treatment with Rifampin alone [73].

Reciprocal Benefits

The above findings show that GSH supplementation strengthens host defenses against *M. tb* by enhancing the immune response and reducing oxidative stress. For individuals with LTBI, this may help prevent progression to active TB. Similarly, for those with active TB, GSH, along with anti-TB drugs, may improve treatment outcomes. In both cases, the ability of GSH to reduce the levels of oxidative stress may also help prevent the onset of depression, which is often linked to chronic inflammation. This shows a potential reciprocal relationship in which reducing oxidative stress not only helps prevent depression but also decreases susceptibility to severe tuberculosis. While current evidence remains preliminary, these findings support the possibility that targeting glutathione restoration may modify both depressive symptom severity and host antimicrobial capacity. Future controlled clinical trials are needed to determine whether this can meaningfully alter TB outcomes in individuals with comorbid MDD.

Conclusion

The connection between tuberculosis and depression is bidirectional, with each condition increasing the risk of the other through biological, psychological, and social mechanisms. This paper specifically highlights glutathione depletion as a biologically significant link between MDD and impaired immunity to *Mycobacterium tuberculosis*. Depression is associated with disrupted glutathione synthesis and metabolism through reduced cysteine availability, diminished GPx activity, and mitochondrial dysfunction. These combined effects increase oxidative stress and chronic inflammation. Effective control of *M. tb* depends on tightly regulated redox balance, macrophage function, and Th1-mediated immune responses. Therefore, GSH depletion in individuals with MDD creates a vulnerable immunological environment that compromises host defense against this intracellular pathogen.

Successful immune control of tuberculosis requires regulated oxidative killing of the pathogen while safeguard-

Table 1. Summary of the mechanisms involved in MDD and TB.

	Major depressive disorder (MDD)	Tuberculosis (TB)
Glutathione (GSH)	GSH depletion occurs due to impaired cysteine uptake, decreased GPx activity, and mitochondrial dysfunction.	GSH depletion leads to impaired macrophage activation and ROS regulation.
Oxidative Stress	Increased ROS due to reduced mitochondrial respiration.	Excess ROS leads to impaired immune cell function.
Cytokine Dysregulation	Chronic low-grade inflammation with increased IL-6, TNF-α, and CRP. IFN-γ is reduced due to low GSH.	Macrophage activation and granuloma formation are dysfunctional due to decreased IFN-γ and TGF-β. As a result, TB outcomes are worsened due to decreased Th1 immunity.
Regulatory (T_{reg}) Cell Function	Reduced PI3K-Akt-mTOR signaling decreases neuronal survival. It also contributes to increased T_{reg} immunosuppression through TGF-β release from activated platelets.	TB leads to an increase in FoxP3+ T_{reg} cells. Decreased PI3K-Akt-mTOR signaling shifts T-cell differentiation towards T_{reg} cells, leading to impaired *M. tb* clearance.
PI3K-Akt-mTOR Pathway	The PI3K-Akt-mTOR pathway is downregulated in individuals with MDD.	The PI3K-Akt-mTOR pathway is downregulated in T-cells, which leads to T_{reg} expansion and reduced effector T-cell function.
Mitochondrial Dysfunction	Decreased oxidative phosphorylation and increased electron leakage lead to a buildup of excess ROS.	Mitochondrial dysfunction disrupts ROS-mediated killing mechanisms carried out by activated macrophages.
Platelet Activation	Increased platelet activation and TGF-β release inhibit enzymes involved in GSH synthesis.	Accumulation of platelets in granulomas leads to increased release of PF4 and TGF-β. This leads to impaired macrophage activation and IFN-γ secretion.
Clinical Risk and Susceptibility	MDD increases susceptibility to other infections due to weakened immune response and chronic inflammation.	TB severity and progression worsen when host immunity is compromised.
Therapeutic Considerations	NAC or liposomal GSH may improve redox balance and depressive symptoms. Ketamine may upregulate mTOR.	Adjunct therapy may improve macrophage activation and function to increase *M. tb* clearance from the host.

ing immune cells through adequate antioxidant defenses. In the setting of MDD, reduced intracellular GSH limits the ability of immune cells to regulate oxidative stress, disrupts cytokine signaling such as interferon-γ production, and impairs macrophage antimicrobial activity. These mechanisms provide a biological explanation for the increased susceptibility to tuberculosis observed in individuals with depression and the greater risk of severe disease (Table 1). Notably, this association cannot be attributed to behavioral factors alone and instead reflects a shared pathophysiological pathway linking mental health and vulnerability to infectious disease.

These results have meaningful clinical and public health relevance, as depression is common in populations at high risk for tuberculosis and often remains underdiagnosed or undertreated. The co-occurrence of depression and tuberculosis is associated with impaired immune responses, delayed diagnosis, reduced adherence to therapy, and worse outcomes. Recognizing depression as an immunological modifier highlights the importance of care that addresses both mental health and biological vulnerability. We propose that glutathione depletion represents a key biological link between depression and increased susceptibility to tuberculosis. Rather than acting as separate comorbid conditions, MDD and TB may share common deficits driven by mitochondrial dysfunction and redox imbalance. Recognizing this connection may help guide the development of integrated therapeutic strategies that address both mental health and infectious disease outcomes.

There is emerging evidence that therapies targeting glutathione restoration may improve outcomes in this context. Supplementation with N-acetylcysteine or liposomal glutathione has demonstrated the ability to reduce oxidative stress, improve depressive symptoms, and support antimicrobial immunity. Although these approaches are not substitutes for standard anti-tuberculosis therapy, these interventions may serve as valuable adjuncts for strengthening host defenses against tuberculosis in individuals with underlying depression.

This study may have some limitations, including reliance on observational and preclinical studies and a limited number of clinical investigations directly examining glutathione modulation in patients with comorbid MDD and tuberculosis. As a result, causal relationships could not be

definitively established. Our findings in this literature review are based on previously published literature, there may be publication bias. Further research is needed to determine the clinical significance of glutathione depletion in populations affected by both depression and tuberculosis and to evaluate whether restoring redox balance improves disease outcomes.

Collectively, available evidence suggests that depression-associated glutathione dysregulation may contribute to impaired immune control of tuberculosis. Integrating mental health care with strategies that address oxidative stress may offer a more comprehensive approach to reducing tuberculosis burden and improving outcomes in vulnerable populations.

Availability of Data and Materials

Not applicable.

Author Contributions

MA and VV designed the research study; MA, MH, FM, and AS performed the research; MA, MH, FM, and AS have been involved in drafting the manuscript; all authors have been involved in revising the manuscript critically for important intellectual content. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Figures were created using BioRender. The authors have no financial or personal relationship with BioRender, and the use of this tool does not imply any endorsement.

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