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# Neuroinflammatory Mechanisms in Treatment-Resistant Depression: A Systematic Review

**Farina Masood**

MS Clinical Psychology, Department of Psychology, Foundation University Islamabad

***Abstract***

*Treatment-resistant depression TRD defined as the failure to achieve an adequate response after at least two antidepressant trials of sufficient dose and duration affects nearly one-third of patients with major depressive disorder MDD and emerging evidence implicates dysregulated neuroinflammatory processes in its pathophysiology, potentially explaining the limited efficacy of conventional monoamine-based therapies. This systematic review synthesizes current evidence on neuroinflammatory mechanisms in TRD, focusing on peripheral inflammatory biomarkers, central microglial activation, blood-brain barrier dysfunction, and the therapeutic implications of targeting inflammation. A comprehensive search of PubMed MEDLINE, PsycINFO, Embase the Cochrane Library and Web of Science identified studies published between January 2005 and December 2025 reporting inflammatory biomarkers, neuroimaging findings, or anti-inflammatory interventions in adults with TRD or MDD with inflammatory subgroup analyses, and study quality assessed using the Newcastle Ottawa Scale, the Cochrane Risk of Bias 2 tool, and the GRADE framework. A total of 23 studies met the inclusion criteria, including observational studies, randomized controlled trials, neuroimaging studies, translational studies, and theoretical reviews, with consistent findings showing elevated levels of interleukin 6 (IL-6), C-reactive protein CRP and tumor necrosis factor alpha (TNF-alpha) in TRD and MDD patients compared to healthy controls. At the same time, TSPO PET neuroimaging demonstrated increased microglial activation in the prefrontal cortex, anterior cingulate cortex, and insula, and evidence suggested that blood-brain barrier disruption facilitates peripheral cytokine entry into the central nervous system. Anti-inflammatory agents, including infliximab, celecoxib, and ketamine, showed greater efficacy in patients with elevated baseline inflammatory markers. Overall, neuroinflammation represents a mechanistically coherent and clinically actionable subtype of TRD, and inflammatory biomarkers, particularly IL-6 and CRP, hold promise for patient stratification and personalized treatment approaches. Future research should prioritize biomarker-stratified prospective trials of targeted immunotherapy in well-defined TRD populations.*

***Keywords:*** *treatment-resistant depression, neuroinflammation, cytokines, interleukin-6, TNF-alpha, C-reactive protein, microglia, blood-brain barrier, TSPO-PET, anti-inflammatory therapy*

## 1. Introduction

Major depression disorder is still among the most common and crippling psychiatric disorders in the world, which causes high global burden of disease. In spite of a very rich pharmacological development and the rich selection of antidepressant agents, a significant percentage of the patients show no sufficient remission. About a third of patients with MDD show non-response to antidepressant treatment with a recurring pattern and progressive functional impairment (Souery et al., 2007). This clinical fact defines treatment-resistant depression, traditionally, which is the inability to reach a satisfactory response despite at least two properly dosed and sufficiently long courses of antidepressant agent (Souery et al., 2007).

The most dominant neurobiological paradigm that has been used in traditional antidepressant development is a monoamine hypothesis, which explains depressive disease through a lack of either serotonergic, noradrenergic, or dopaminergic neurotransmission. Yet, this model seems to be growing unproductive in explaining the entire gamut of depressive psychopathology. The consistent failure of conventional treatments in TRD has catalyzed investigations into alternative biological mechanisms, with immune dysregulation and neuroinflammation emerging as the most robustly supported candidates (Miller & Raison, 2016; Troubat et al., 2021).

The inflammatory hypothesis of depression postulates that sustained activation of the innate immune system, elevated circulating pro-inflammatory cytokines, microglial activation within the brain, and disruption of the blood-brain barrier synergistically engender and sustain depressive symptoms that resist monoamine-targeting drugs (Miller & Raison, 2016). It is now being speculated that MDD represents, at least in part a disorder where dysregulated cytokine networks are central aspects of pathophysiology, and that multiple classes of antidepressants can act at least in part by immunomodulatory pathways that are not based on the traditional effects of each neurotransmitter (Köhler et al., 2017). The study of 82 studies on the topic of peripheral IL6, TNF-alpha and a number of other inflammatory measures established a strong empirical basis of the inflammatory hypothesis, suggesting that peripheral IL6, TNF-alpha and several other inflammatory markers are significantly higher in MDD compared to healthy controls (Köhler et al., 2017).

The clinical importance of this framework is great. If neuroinflammation underlies a distinct biologic phenotype of TRD, then continued reliance on conventional antidepressants in this subgroup may be ineffectual and may unnecessarily delay access to appropriate therapies. The discrimination and recognition of neuroinflammatory pathways in TRD provide an excellent avenue to precision psychiatry of a population with limited evidence-based alternatives. In this manner, it is shown that this systematic review summarizes evidence based on peripheral biomarker research, central neuroimaging research, translational research, and clinical trials on anti-inflammatory interventions, and speculates on implications of such evidence on personalized treatment strategies in TRD.

## 2. Methods

### 2.1 Eligibility Criteria

Research could be included in the study provided that it: (1) used adults aged 18 years or older as participants and diagnosed them with TRD, which is non-response to 2 or more adequate antidepressant trials, or (2) used MDD cohorts with specific TRD or inflammatory subgroup analysis; and (3) was published in English. Basic mechanistic and theoretical research studies also were included where they added crucial pathophysiological background not found in more recent empirical studies.

Articles were not included in the study when they involved participants with active autoimmune disease, cancer or infection processes that are known to confound inflammatory measures significantly or they were a case study or editorial or grey literature that was not peer-reviewed.

### 2.2 Information Sources and Search Strategy

The electronic databases that were searched in a systematic manner and which had a strong indexing of psychiatric and biomedical literature included PubMed/MEDLINE, PsycINFO, Embase, the Cochrane Library, and Web of Science. The last 20 years' studies were included in the search i.e. from January 2005 to December 2025. The last update of the search was done in January 2026. The following string was used with the help of Boolean logic:

("treatment-resistant depression" OR "refractory depression" OR "TRD") AND ("neuroinflammation" OR "inflammation" OR "cytokines" OR "interleukin" OR "IL-6" OR "TNF-alpha" OR "CRP" OR "C-reactive protein" OR "microglia" OR "blood-brain barrier" OR "TSPO" OR "translocator protein" OR "glial activation")

Included study reference lists and relevant systematic reviews were manually screened in order to identify more eligible works.

### 2.3 Data Extraction and Study Selection.

Before evaluating the full-texts, two independent reviewers screened titles and abstracts and rated them based on a standardized inclusion-exclusion checklist. Any discrepancies were adjudicated by a third reviewer. Interpreted study design, sample size, definition of TRD or MDD, inflammatory outcome measure, sample versus control group, key results, and reported effect sizes were tabulated in a structured extraction form.

### 2.4 Quality Assessment

The quality of observational studies was assessed using the Newcastle-Ottawa Scale; the level of seven or more out of nine points reflected high methodology. Randomized controlled trials were evaluated using Cochrane Risk of Bias 2 tool in five areas; randomization, allocation concealment, blinding, outcome data completeness, and selective reporting. The certainty of the evidence was assessed based on the GRADE pyramid.

### 2.5 Data Synthesis

Considering high levels of heterogeneity in the study designs, characteristics of the participants, biomarkers being studied and the outcome measures, a formal meta-analysis was considered impossible. Results have been synthesized in the form of narratives and thematically arranged

into four topics: (a) peripheral inflammatory biomarkers, (b) central neuroinflammatory mechanisms and neuroimaging, (c) blood-brain barrier disruption and (d) anti-inflammatory treatment interventions.

## 3. Results

### 3.1 Study Selection

Database search after elimination of duplicates provided 1,847 records. After screening title and abstract, 214 full-text articles were evaluated in terms of eligibility. Twenty-three articles met all the inclusion criteria. The analyzed cohort consisted of 8 observational studies and meta-analyses, 4 randomized controlled trials, 4 neuroimaging studies, 3 translational and mechanistic studies, and 4 theoretical or narrative reviews which gave important pathophysiological context.

*(Insert Figure 1 here)*

### 3.3 Peripheral Inflammatory Biomarkers in TRD

#### 3.3.1 Interleukin-6

The most uniformly involved biomarker of inflammation was IL-6 in both MDD and TRD. A cumulative meta-analysis of 58 studies in which more than 5,000 patients were included showed that there is a strong and reproducible relationship between IL-6 elevation and depression, and the effect is strengthened by additional data (Haapakoski et al., 2015). This review proved the consistency of IL 6 and CRP as most reliable elevated markers in MDD and TNF -A was inconsistently associated and this was greatly due to high between-study heterogeneity which is a significant caveat that should be used to interpret TNF -A as a universal MDD biomarker (Haapakoski et al., 2015).

In the TRD subgroup in particular, Chamberlain et al. (2019) enlisted 252 participants in four groups, including 102 TRD patients, 48 treatment-responsive non-depressed patients, 48 unmedicated depressed patients, and 54 healthy controls and reported that the BMI-adjusted CRP was significantly high in the TRD group compared to the healthy controls ($p= 0.007$, Cohen $d=0.47$). There was neither significant CRP increase in the treatment-responsive nor unmedicated groups. This selective increase pattern indicates the inflammatory pattern is not just a symptom of active depression, this pattern may outline the treatment resistance. Vegetative depressive symptoms, BMI, state anxiety, and childhood adversity were found to be the clinical phenotypes with the highest associations with high CRP in TRD (Chamberlain et al., 2019).

#### 3.3.2 Peripheral Cytokine Profiles.

A meta-analysis of 82 studies by Köhler et al. (2017) which included 3,212 MDD patients and 2,798 controls revealed that peripheral concentrations of ten immune markers were strongly elevated in MDD, such as IL-6, TNF-a, IL-10, soluble IL-2 receptor, IL-13, IL-18, IL-12, IL-1 receptor antagonist, soluble TNF receptor 2 and CCL2. Conversely, interferon gambling was much less in MDD compared to controls (Hedges, $g = -0.477$, $p = 0.043$). Notably, IL 1B, IL 2, IL 4, IL 8 and transforming growth factor-b1 showed no significant difference which highlights a selective and not extensive profile of immune activation. This particularity has consequences both on the choice of biomarkers in medical practice and the reasonable construction of specific antiinflammatory interventions (Köhler et al., 2017).

A meta-analysis of 37 studies (13,541 depressed patients and 155,728 controls) revealed that low-grade inflammation (CRP >3mg/L -1) was found in about 27 percent of patients with MDD, which is much greater than the average population (Osimo et al., 2019). This figure highlights the importance of a clinical relevance of an inflammatory phenotype which can be affected by anti-inflammatory interventions, particularly considering the results of Chamberlain et al. (2019) who claim that the inflammatory phenotype is more prevalent among the TRD population (Chamberlain et al., 2019).

### 3.3.3 TNF-α as a Therapeutic Target

Haapakoski et al. (2015) reported disparate TNF-alpha readings between studies (Haapakoski et al., 2015). On a therapeutic scale, Raison et al. (2013) have presented a historic double-blind, placebo, and randomized controlled trial in which intravenous infliximab, which is an anti-TNF-alpha monoclonal antibody, was used in 60 patients who were having TRD (Raison et al., 2013). The overall cohort of unselected groups did not determine a better performance of infliximab compared to placebo. Nevertheless, in the pre-specified population that had baseline CRP over 5mg/L -1, the infliximab response rate was 62% compared to 33% in the placebo arm which is a statistically significant difference of clinical significance. It was this biomarker-stratified outcome that defined the principle on which the efficacy of anti-inflammatory treatments in TRD depends on the availability of preexisting inflammatory phenotype and was the catalyst to the wider body of inflammation-stratified antidepressant trials (Raison et al., 2013).

## 3.4. Central Neuroinflammatory Mechanisms.

### 3.4.1 Microglial Activation and M1 Polarization

Microglia constitute the resident immune population of the central nervous system and function as the principal mediators of neuroinflammation. Their morphology and function are reconfigured in response to inflammatory stimuli, albeit assuming physiological conditions they are in a ramified surveillance phenotype. Troubat et al. (2021) elaborated in detail how microglial activation toward the pro-inflammatory M1 phenotype, in concert with interactions with reactive A1 astrocytes, provokes a cascade of neurotoxic cytokine release that culminates in neuronal injury, suppression of BDNF expression, perturbation of serotonin metabolism via IDO activation and diversion of the kynurenine pathway, and impairment of hippocampal neurogenesis (Troubat et al., 2021). All these downstream effects are mechanistically relevant to the clinical presentation of treatment-resistant depression (TRD) such as anhedonia, cognitive impairment, and poor response to antidepressants.

The conceptual framework behind the translation of peripheral inflammation into central behavioral change was given by Dantzer et al. (2008) and consists of the following cascade of immune activation to cytokine-mediated signaling to the brain and the resultant sickness behavior that when persisted significantly overlaps with clinical depression (Dantzer et al., 2008). As a continuation of this model, Miller and Raison (2016) added an evolutionary perspective, which suggests that the cytokine-to-depression pathway was an evolutionary response that has been coopted by modern psychosocial stressors in order to induce chronic neuroinflammatory conditions that are the basis of TRD (Miller & Raison, 2016). Their theoretical framework delineates three distinct pathways through which peripheral inflammatory signals traverse the blood-brain barrier and influence the central nervous system: (1) a humoral pathway involving cytokine traversal of leaky blood-brain barrier regions, particularly at

circumventricular organs; (2) a neural pathway wherein cytokines bind to peripheral afferent nerve fibers, including the vagus nerve; and (3) a cellular pathway comprising the transmigration of activated peripheral monocytes across the blood-brain barrier. The framework of immunoneuropsychiatric presented by Pape et al. (2019) suggests a wider context of the immune-stratified descriptors of diagnosis and treatment of psychiatric disorders, including TRD.

### 3.4.2 TSPO-PET Neuroimaging of Microglial Activation

The 18 kDa translocator protein, expressed at high levels by activated microglia and reactive astrocytes, serves as the principal molecular target for in vivo neuroimaging of neuroinflammation in psychiatric patients using positron emission tomography. A controlled neuroimaging case-case study of 20 MDD patients and 20 healthy control condition participants by Setiawan et al. (2015) demonstrated that TSPO binding in the prefrontal cortex, anterior cingulate, and insula was about 30 per cent higher in patients who were in an active depressive episode compared to healthy controls (Setiawan et al., 2015). This provided the first robust in-vivo confirmation of localized neuroinflammation in depression via this methodology.

A review of TSPO-PET studies conducted by Gritti et al. (2021) confirmed that high TSPO binding in the prefrontal cortex, anterior cingulate cortex, and hippocampus is the most reliable neuroimaging result of MDD, but suggested that the methodology is inconsistent because of differences in radiotracer affinity and inter-individual differences in the binding affinity of TSPO that depend on the rs6971 polymorphism (Gritti et al., 2021).

The study by Attwells et al. (2020) provided a considerable gap in translation between patients with a high baseline TSPO binding and those with celebrity coxib administration showed that the use of the drugs achieved significant changes in the TSPO binding volume, supplemented by decreases in depressive symptom scores in the patients (Attwells et al., 2020). This constituted direct neuroimaging evidence that COX-2 inhibition reverses central microglial activation in MDD. However, Schubert et al. (2021) found that a small, statistically insignificant change in TSPO binding occurred in their depression group, and importantly found no relationship between TSPO binding and serum CRP or BMI (Schubert et al., 2021). This dissociation between peripheral and central inflammatory indices constitutes an important methodological and clinical consideration, suggesting that normalization of peripheral biomarkers cannot be presumed to mirror resolution of central neuroinflammation and that independent assessment of both compartments is warranted (Schubert et al., 2021).

### 3.4.3 Kynurenine Pathway and HPA Axis Interactions

Troubat et al. (2021) described the kynurenine pathway as a pivotal nexus linking neuroinflammation to serotonergic dysfunction in TRD (Troubat et al., 2021). Pro-inflammatory cytokines, particularly interferon-γ and TNF-α, upregulate indoleamine 2,3-dioxygenase, which diverts tryptophan metabolism away from serotonin synthesis toward the production of neurotoxic kynurenine metabolites, including quinolinic acid. This mechanistic process can directly explain why the use of selective serotonin reuptake inhibitor (SSRI) may be ineffective in patients with increased baseline inflammation: the inflammatory stimulation of IDO is constantly emptying the tryptophan substrate necessary to produce serotonin, making serotonin reuptake inhibition therapeutically ineffective.

Hassamal (2023) detailed the bidirectional relationship between HPA axis dysregulation and neuroinflammation in TRD (Hassamal, 2023). Persistent stress triggers the HPA axis and increases cortisol, which is paradoxical because it stimulates the resistance of glucocorticoids in immune cells. Such resistance undermines cortisol's normative anti-inflammatory suppression, permitting unchecked production of inflammatory cytokines. The ensuing coexistence of hypercortisolemia and glucocorticoid resistance sustains both HPA dysregulation and neuroinflammation in a mutually reinforcing cycle, thereby constituting a core pathophysiological feature perpetuating TRD (Hassamal, 2023).

### 3.5 Blood-Brain Barrier Disruption in TRD

The blood brain barrier acts as the main anatomical point of contact with the peripheral immune environment and the central nervous system parenchyma. In TRD, converging evidence supports a model in which blood-brain barrier compromise facilitates the translocation of pro-inflammatory signals from systemic circulation into the brain parenchyma, amplifying central neuroinflammation and engendering pathological conditions sustaining treatment resistance.

A study integrating murine models with post-mortem human tissue analysis revealed that social stress caused quantifiable neuro-vascular pathology and blood-brain barrier dysfunction with resultant increases in permeability coupled with the same behavior in animals and identical effects in post-mortem human brain tissue in depressed individuals (Menard et al., 2017). This study associated psychosocial stressors with structural blood-brain barriers pathology in a direct and mechanistic connection between environmental factors and neurobiological maintenance of depression.

The molecular mechanism of TNF -induced blood-brain barrier disruption was described by Cheng et al. (2018), who showed that TNF -induced structural impairment of the integrity of claudin -5 and ZO -1 tight junction proteins in a mouse model, which supports and sustains depressive-like behavior (Cheng et al., 2018). These findings furnish a molecular explanation for why elevated circulating TNF-α in TRD patients may have consequences extending beyond peripheral immune activation to directly perpetuate central neuroinflammation through blood-brain barrier compromise.

Althubaity et al. (2021) provided in-vivo MRI-based evidence in 51 participants that choroid plexus enlargement in depressed patients was associated with neuroinflammation markers and reduced blood-brain barrier permeability, thereby identifying the choroid plexus as a critical site of inflammatory regulation and offering a clinically accessible neuroimaging marker of blood-brain barrier disruption in depression (Althubaity et al., 2022).

### 3.6 Anti-Inflammatory Therapeutic Strategies in TRD

#### 3.6.1 TNF-α Inhibition

Raison et al. (2013) infliximab randomized controlled trial is the only most convincing evidence of the principle of inflammatory subtype in TRD (Raison et al., 2013). The biomarker stratified response pattern, in which patients with CRP more than 5mg/L responded twice as often than placebo with the remainder of the sample not responding at all, determined that the efficacy of anti inflammatory treatment depends on pre-existing inflammation. This observation has fundamentally transformed the fact that the field recognizes that TRD is not a uniform entity and

that inflammatory phenotyping has to be done first before the allocation of anti-inflammatory treatment (Raison et al., 2013). This means that the lack of a general effect of treatment in unselected populations of TRD does not invalidate the possibility of usefulness of anti-inflammatory interventions in the inflammatory subtype, and that lack of effect in unselected samples should not be used to reject the inflammatory hypothesis.

### 3.6.2 COX-2 Inhibition and Broader Anti-inflammatory Evidence

In a meta-analysis of 30 randomised controlled trials of 1,610 subjects, Bai et al. (2020) discovered that the anti-inflammatory agents as a group demonstrated a significant effect in depressive symptoms reduction, when compared to placebo, with the highest effect sizes found in subgroups with high baseline levels of inflammatory markers (Bai et al., 2020). This dose-response interaction between pre-therapy inflammation and the response to anti-inflammatory treatment is an added support to the inflammatory subtype model. Attwells et al. (2020) specifically demonstrated that celecoxib reduced TSPO-PET binding concomitant with symptomatic improvement in patients with elevated baseline neuroinflammation, thereby providing direct neuroimaging evidence that COX-2 inhibition reverses central microglial activation in conjunction with clinical benefit (Attwells et al., 2020).

### 3.6.3 Ketamine and Esketamine

Ketamine and esketamine have emerged as the most effective of the rapid-acting antidepressants in TRD and are traditionally explained by the NMDA antagonism and consequently AMPA-releases of BDNF. In a systematic review of 12 studies, Sukhram et al. (2022) established that ketamine antidepressant effect in TRD was systematically associated with decreases in the IL-6 and TNF-A, and that increment in the baseline inflammatory condition predicted the enhancement of the magnitude of antidepressant effects, establishing ketamine as a treatment of unique utility in the inflammatory -type TRD (Sukhram et al., 2022). Johnston et al. (2023) argued that ketamine concurrently addresses glutamatergic dysregulation, stress axis hyperactivity, and neuroinflammation in TRD, with its anti-inflammatory mechanism contributing substantively to its rapid onset of action (Johnston et al., 2023). Halaris and Cook (2023) analyzed ketamine and esketamine through a neuroinflammatory prism, where they found that both agents exert anti-inflammatory effects, which might comprise a substantial element of their relative efficacy compared to other conventional antidepressants in TRD, and recommended future studies using an inflammatory-phenotyped cohort (Halaris & Cook, 2023).

### 3.6.4 Electroconvulsive Therapy

The use of electroconvulsive therapy continues to be among the most effective treatment of severe TRD. Yrondi et al. (2018) reported a systematic review of 18 studies with a neuroinflammatory profile of ECT showing that in responders to ECT, it caused an immediate transient increase in IL-6 levels after a session of ECT, which gradually returned to normal throughout the treatment (Yrondi et al., 2018). It was also found that pre-treatment levels of IL-6 were predictive of response to the treatment. Jarventausta et al. (2017) provided prospective cohort evidence that IL-6-based changes during the ECT course reflected a clinical response directly, and early IL-6 changes predicted a patient who was most likely to get clinical benefit due to the entire course of treatment (Järventausta et al., 2017). Together, these results make IL-6 dynamics one of the possible biomarkers to monitor and predict ECT response in TRD to provide a clinically viable way of early treatment assessment.

## 4. Discussion

### 4.1 Convergent Evidence for an Inflammatory Subtype of TRD

The collective findings of this systematic review corroborate the existence of a biologically distinct inflammatory subtype of TRD, characterised by elevated circulating CRP, IL-6, and TNF-α, demonstrable central microglial activation on TSPO-PET imaging, structural blood-brain barrier compromise, and preferential clinical response to anti-inflammatory rather than monoamine-targeting interventions. This discussion and cross-peripheral biomarker literature (Chamberlain et al., 2019; Haapakoski et al., 2015; Köhler et al., 2017; Osimo et al., 2019), neuroimaging research (Attwells et al., 2020; Gritti et al., 2021; Setiawan et al., 2015), and even clinical trials (Bai et al., 2020; Raison et al., 2013).

The theoretical work of Dantzer et al. (2008), Miller and Raison (2016) and Pape et al. (2019) serves as the mechanistic scaffold in which the presented empirical evidence can be arranged into a consistent pathophysiological story (Dantzer et al., 2008; Miller & Raison, 2016; Pape et al., 2019). Troubat et al. (2021) and Hassamal (2023) furnish detailed accounts of how microglial activation, kynurenine pathway dysregulation, and HPA-immune bidirectionality each contribute to the maintenance of TRD in patients exhibiting an inflammatory phenotype (Hassamal, 2023; Troubat et al., 2021). Together, these contributions establish neuroinflammation as not merely an epiphenomenon of depression but as an active pathophysiological driver capable of sustaining treatment resistance independently of monoamine system dysregulation.

### 4.2 Biomarker-Guided Treatment as Clinical Priority

The cumulative findings considered lead to one practical clinical implication, which is that inflammatory phenotyping should be integrated in the evaluation of all patients who meet the predetermined criteria of treatment-resistant depression (TRD). The most practice-friendly clinically relevant candidates to be measured regularly are C -reactive protein (CRP) and interleukin -6 (IL -6 ). Chamberlain et al. (2019) used a CRP level more than 1mg/L to distinguish between TRD and anti-inflammatory major depressive disorder (MDD), and Raison et al. (2013) used a CRP level over 5mg/L to identify eligibility to anti-inflammatory treatment in the infliximab trial (Chamberlain et al., 2019; Raison et al., 2013). Osimo et al. (2019) revealed a CRP above 3mg/L (typically considered as a clinical cut-off of low-grade inflammation) in about 27 per cent of MDD patients (Osimo et al., 2019). Even though these thresholds offer a practical system of clinical application, direct comparative analyses on their predictability of an anti-inflammatory response in TRD specifically are an unexplored research gap.

The belief that the choice of treatment should be influenced by biomarkers is supported by the literature on ketamine discussed in this paper. Sukhram et al. (2022) demonstrated that the baseline status of inflammation is a predictor of ketamine response in TRD, indicating that inflammatory phenotyping before ketamine could be a predictor of patients who would respond best and therefore maximize the utilization of limited resources associated with specialist care in health care systems that use ketamine (Sukhram et al., 2022).

### 4.3 The Central-Peripheral Inflammatory Dissociation

The outstanding problem that is critically unresolved and highlighted by this review is the discrepancy between peripheral biomarkers and central neuroimaging indices of inflammation. The study conducted by Schubert et al. (2021) had no correlation between serum CRP and

translocator protein-positron emission tomography (TSPO-PET) binding with the reported depression cohort (Schubert et al., 2021), where Gritti et al. (2021) found substantial inconsistency in the radiotracer techniques in other TSPO-PET studies (Gritti et al., 2021). This dissociation cautions against assuming that a normal peripheral CRP excludes central neuroinflammation, or conversely that an elevated CRP necessarily signifies active microglial activation.

This dissociation can be explained by a number of mechanisms, such as the ability of the blood-brain barrier to limit the entry of peripheral cytokines despite a partial loss of function, spontaneous central glial activity independent of systemic inflammation, and natural methodological variability of the TSPO imaging reported by Gritti et al. (2021). As a result, peripheral biomarkers, and neuroimaging seemingly describe, in part, different mechanisms of inflammation, meaning that a multimodal approach to the inflammatory phenotyping of TRD will eventually require a combination of available blood markers with, where possible, neuroimaging validation (Gritti et al., 2021).

### 4.4 Neuroplasticity and the Inflammatory Brake

Neuroinflammation and neuroplasticity represent mechanistically antagonistic processes in TRD. Troubat et al. (2021) provided detailed evidence that M1 microglial activation suppresses brain-derived neurotrophic factor (BDNF) expression and impairs hippocampal neurogenesis, thereby undermining the cellular substrates upon which conventional antidepressants rely for therapeutic efficacy (Troubat et al., 2021). Hassamal (2023) also demonstrated how chronic resistance to glucocorticoids enhances this neuroplastic suppression by eliminating the physiological anti-inflammatory cortisol block on the production of cytokines (Hassamal, 2023). The resulting condition undermines the fundamental therapeutic conditions of antidepressant efficacy, intact serotonergic neurotransmission, normal BDNF signaling, and intact neuroplasticity, through the ubiquitous neuroinflammatory environment, which is the cause of the observed clinical state of compounded treatment failure across the successive antidepressant trials in inflammatory-subtype TRD.

The clinical implication of this paradigm is that in inflammatory-subtype TRD patients, anti-inflammatory intervention may have to go hand in hand or come before conventional antidepressant therapy in order to replenish the neuroplastic substrate necessary to respond to treatment. Attwells et al. (2020) established that celecoxib decreased the TSPO binding as well as depressive symptoms simultaneously, which empirically supports this mix of therapy (Attwells et al., 2020).

### 4.5 Limitations of the Current Evidence.

There are a number of limitations associated with the current evidence base that should be mentioned explicitly. To begin with, the heterogeneity in definitions of TRD across studies such as the number of failed trials required to define it and the definition of trial adequacy lowers the comparability of inflammatory profile and makes the meta-analysis of synthesis a difficult task. Second, observational investigations were inconsistent in excluding the presence of the influential confounders of inflammation including obesity, smoking and comorbidity of inflammatory medical conditions which could have inflated estimates of the prevalence and the magnitude of depression-specific inflammation. Third, most of the reviewed anti-inflammatory randomized controlled studies were done in general MDD cohorts and not rigorously defined

high-risk TRD populations and hence the direct generalization of effects-size estimates to clinical practice of TRD. Fourth, there was relatively limited sample sizes in TSPO-PET studies that were included in this review, and the variety of radiotracers that were used, in conjunction with the effect of the rs6971 polymorphism on the affinity of TSPO binding, significantly complicates cross-study comparisons, as reported by Gritti et al. (2021) and Schubert et al. (2021). Fifth, the prevalence of cross-sectional designs in the peripheral biomarker literature limits causal inferences on whether high inflammatory states predispose, trigger, or are consequences of treatment resistance.

## 5. Conclusions

Such cumulative, multimodal support on the view that neuroinflammatory dysregulation is a primary, action-logically consistent, and mechanistically valid, pathway in treatment-resistant depression is delivered by this systematic review of 23 established studies. There is strong specific association between peripheral concentrations of IL-6 and CRP and TRD compared to healthy controls, as well as to treatment-responsive patients (Chamberlain et al., 2019; Haapakoski et al., 2015). Greater pro-inflammatory cytokine signature, including marked TNF -a increase, is validated in large meta-analytic samples (Köhler et al., 2017). Microglial activation is demonstrable in vivo in the prefrontal cortex, anterior cingulate cortex, and insula via TSPO-PET imaging (Gritti et al., 2021; Setiawan et al., 2015), and is reversible with anti-inflammatory treatment (Attwells et al., 2020). Breaking the blood-brain barrier, which is mechanistically mediated by tight junction protein degradation mediated by TNF-alpha (Cheng et al., 2018) and neuroimaging of the choroid plexus (Althubaity et al., 2022) and post-mortem tissue studies (Menard et al., 2017) confirms the spread of peripheral inflammation to the CNS.

Anti-inflammatory interventions show selectively increased effectiveness in patients with higher baseline inflammatory markers: TNF-alpha inhibition with infliximab had 62-percent response rates in CRP-elevated TRD patients compared to 33-percent (placebo) (Raison et al., 2013); anti-inflammatory drugs as a category had a significant antidepressant effect in meta-analysis, with the largest effects seen in high-CRP-groups (Bai et al., 2020); and the ant Electroconvulsive therapy has dynamic effects on IL-6 that monitor and forecast treatment response (Järventausta et al., 2017; Yrondi et al., 2018).

The mechanistic foundations outlined by Dantzer et al. (2008), Miller and Raison (2016), Troubat et al. (2021), Hassamal (2023), and Pape et al. (2019) collectively establish neuroinflammation not as a mere epiphenomenon but as an active pathophysiological driver that sustains treatment resistance by suppressing serotonin synthesis through indoleamine-2,3-dioxygenase activation, impairing BDNF-dependent neuroplasticity, and maintaining hypothalamic-pituitary-adrenal axis dysregulation via glucocorticoid resistance (Dantzer et al., 2008; Hassamal, 2023; Miller & Raison, 2016; Pape et al., 2019; Troubat et al., 2021). The clinical imperative is clear, which is that inflammatory phenotype patients must be placed as a priority in the assessment of inflammatory biomarkers and be treated using biomarker-stratified anti-inflammatory therapy instead of empirical cycling of antidepressants. Future research needs standardized inflammatory phenotyping protocols at the point of TRD designation, prospective randomized controlled trial with inflammatory-subtype TRD patients specifically, validation of composite inflammatory indices and next-generation immunological targets such as IL-6 receptor antagonism, Janus kinase inhibition, and microbiome-targeted interventions.

**Declarations:**

**Ethics Approval and Consent to Participate:** This systematic review did not require ethical approval, as it exclusively synthesized data from previously published peer-reviewed studies and did not involve the recruitment of human participants, the use of animal subjects, the collection of biological specimens, or the processing of identifiable personal data. All primary data were obtained from studies that had independently obtained appropriate ethical clearance at the time of their original conduct. This review was conducted in full accordance with the principles of the Declaration of Helsinki as they apply to secondary research.

**Conflict of Interest Statement:** The author declares that the research was conducted in the absence of any commercial, financial, or personal relationships that could be construed as a potential conflict of interest. No advisory, consultancy, speaker, or honoraria arrangements exist with any pharmaceutical, biotechnology, or healthcare organization with a commercial interest in the subject matter of this review, including manufacturers of anti-inflammatory agents, immunomodulatory therapies, or antidepressant medications discussed herein.

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**Data Availability:** This review did not generate or analyze any primary datasets. The study is entirely based on synthesis of previously published, publicly available peer-reviewed literature. All sources consulted and cited in support of the findings, conclusions, and arguments presented in this review are fully referenced in the reference list. No additional data, datasets, or supplementary materials beyond those described in the manuscript are available or applicable.

**Author contributions:** This systematic review was conducted solely by a single author. The author independently conceptualized the research question and review scope, developed and executed the systematic search strategy across all five databases, performed title and abstract screening and full-text eligibility assessment, conducted quality appraisal of included studies using the Newcastle-Ottawa Scale and Cochrane Risk of Bias 2 tool, synthesized and interpreted the evidence, and drafted, revised, and finalized the manuscript in its entirety. The author approved the final version submitted for publication and accepts full accountability for all aspects of the work.

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*Figure 1. PRISMA 2020 flow diagram*

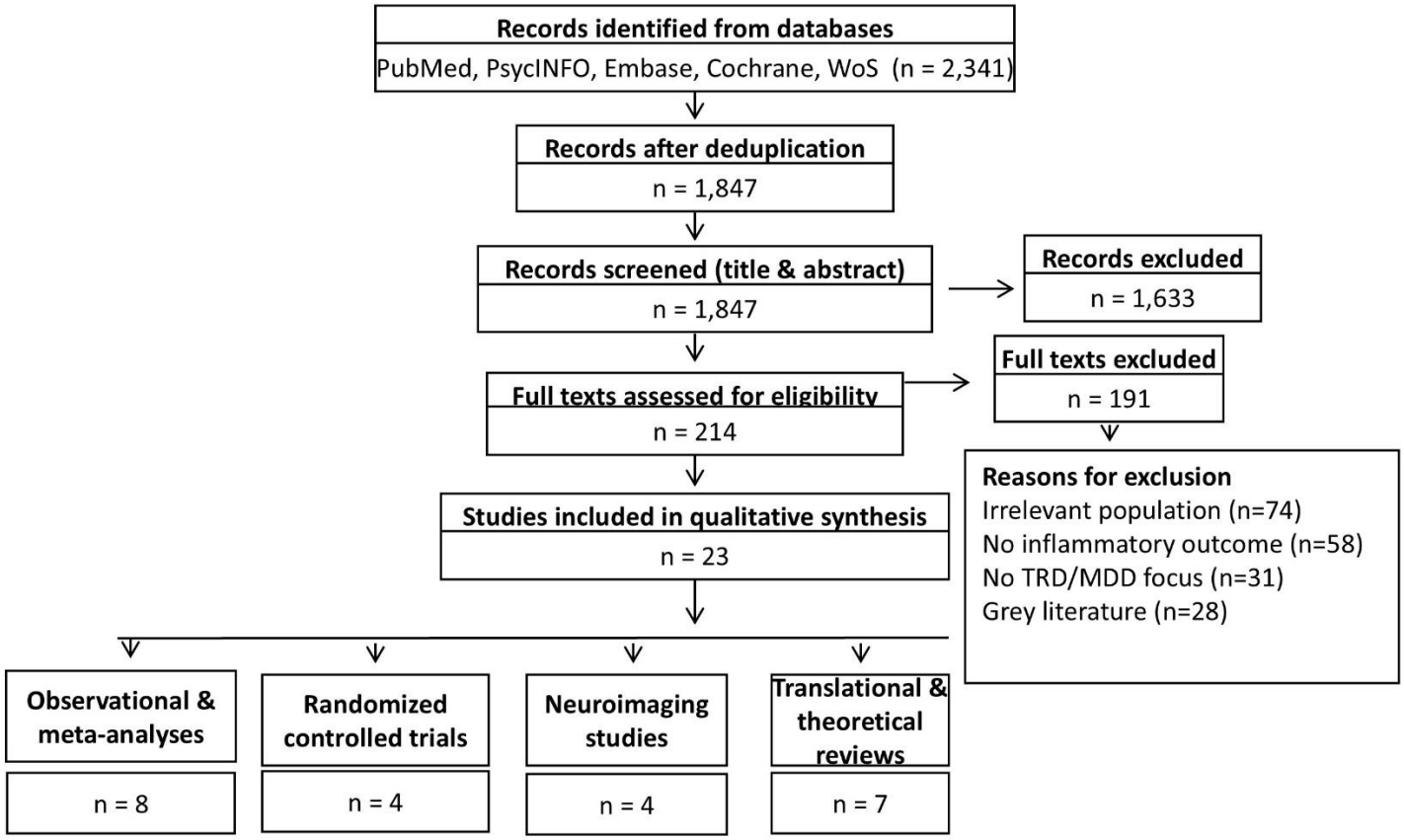

*Table 1. Summary of Included Studies on Neuroinflammation in Treatment-Resistant Depression*

| Author(s) & Year | Study Design | Sample | TRD/MDD Definition | Inflammatory Measures | Main Findings | Quality |
|---|---|---|---|---|---|---|
| Chamberlain et al. (2019) | Case-control | N=252: 102 TRD, 48 treatment-responsive, 48 unmedicated MDD, 54 HC | ≥2 failed antidepressant trials | Peripheral high-sensitivity CRP | BMI-corrected CRP significantly elevated in TRD vs. HC (p=0.007, Cohen's d=0.47); not significant in treatment-responsive or unmedicated groups | NOS: 8/9 |
| Haapakoski et al. (2015) | Cumulative meta-analysis | 58 studies; N>5,000 | MDD including TRD subgroup | IL-6, CRP | IL-6 and CRP robustly elevated in MDD; confirmed from earliest 8 studies; TNF-α showed no consistent association due to heterogeneity | NOS: 8/9 |
| Köhler et al. (2017) | Meta-analysis | 82 studies; N=3,212 MDD, 2,798 HC | MDD vs. healthy controls | IL-6, TNF-α, IL-10, sIL-2R, IL-13, IL-18, IL-12, IL-1RA, sTNFR2, CCL2; IFN-γ reduced | 10 inflammatory markers elevated in MDD; IFN-γ significantly reduced; IL-1β, IL-2, IL-4, IL-8 not significantly altered | NOS: 8/9 |
| Raison et al. (2013) | RCT, double-blind, placebo-controlled | N=60 TRD | ≥2 failed antidepressant trials | TNF-α, hs-CRP, soluble TNF receptors | Infliximab showed no overall benefit; patients with baseline CRP >5 mg/L: 62% response vs. 33% placebo | RoB: Low |
| Setiawan et al. (2015) | TSPO-PET neuroimaging | N=40: 20 MDD, 20 HC | Active depressive episode | TSPO binding potential (microglial activation) | TSPO binding ~30% higher in PFC, ACC, and insula in MDD vs. HC | NOS: 7/9 |
| Gritti et al. (2021) | Neuroimaging systematic review | Multiple TSPO-PET studies | MDD including TRD | TSPO-PET binding potential | Elevated TSPO consistently reported in PFC, ACC, hippocampus; | NOS: 7/9 |

| Author(s) & Year | Study Design | Sample | TRD/MDD Definition | Inflammatory Measures | Main Findings | Quality |
|---|---|---|---|---|---|---|
| | | | | | methodological inconsistency across radiotracers noted | |
| Attwells et al. (2020) | Open-label trial | N=14 MDD | Elevated TSPO at baseline | TSPO-PET binding volume | Celecoxib reduced TSPO binding volume; depressive symptom scores improved | RoB: Moderate |
| Schubert et al. (2021) | TSPO-PET case-control | N=51: MDD vs. HC | MDD including TRD | TSPO-PET via 11C-PK11195 | Modest increase in TSPO binding in MDD not correlated with serum CRP or BMI; suggests central-peripheral inflammatory dissociation | NOS: 7/9 |
| Bai et al. (2020) | Meta-analysis of RCTs | 30 RCTs; N=1,610 | MDD with treatment failure subgroup | Depressive symptom scores; anti-inflammatory efficacy | Anti-inflammatory agents significantly reduced depressive symptoms; larger effects in elevated-CRP subgroups | NOS: 8/9 |
| Osimo et al. (2019) | Meta-analysis | 37 studies; N=13,541 MDD, 155,728 controls | MDD with CRP substudy | CRP levels | Prevalence of CRP >3 mg/L in depression was 27%; significantly higher than healthy controls | NOS: 8/9 |
| Sukhram et al. (2022) | Rapid systematic review | 12 studies | TRD specifically | IL-6, TNF-α post-ketamine | Ketamine reduced pro-inflammatory cytokines in TRD; reductions in IL-6 and TNF-α correlated with antidepressant response; higher baseline inflammation predicted better ketamine response | NOS: 7/9 |
| Troubat et al. | Narrative | — | MDD and TRD | Microglia, cytokines, HPA | M1 microglial polarization | NOS: 7/9 |

| Author(s) & Year | Study Design | Sample | TRD/MDD Definition | Inflammatory Measures | Main Findings | Quality |
|---|---|---|---|---|---|---|
| (2021) | review | | | axis, kynurenine pathway | drives IDO activation, disrupts serotonin metabolism, suppresses BDNF, and impairs hippocampal neurogenesis | |
| Cheng et al. (2018) | Translational animal study | Mouse model | Stress-induced depressive behavior | TNF-α, BBB tight junction proteins claudin-5 and ZO-1 | TNF-α degrades claudin-5 and ZO-1, disrupting BBB integrity and maintaining prolonged depressive-like behavior | N/A |
| Menard et al. (2017) | Translational study with human tissue | Mouse model; post-mortem human tissue | Social stress-induced depression | VEGF, BBB permeability, IL-6 | Social stress induced neurovascular pathology and BBB disruption; findings replicated in post-mortem human brain tissue from depressed individuals | N/A |
| Althubaity et al. (2021) | Neuroimaging case-control | N=51: MDD=26, HC=25 | Active depressive episode | Choroid plexus volume; BBB permeability via MRI | Choroid plexus enlargement associated with neuroinflammation and reduced BBB permeability in MDD | NOS: 7/9 |
| Yrondi et al. (2018) | Systematic review | 18 studies | MDD requiring ECT | IL-6, TNF-α, CRP during ECT | ECT associated with acute IL-6 elevation after early sessions and chronic normalization in responders; pre-ECT IL-6 predicted treatment response | NOS: 7/9 |
| Hassamal (2023) | Narrative review | — | Chronic stress leading to TRD | HPA axis, CRH, cortisol, cytokines | Chronic stress creates self-sustaining HPA-immune loop; glucocorticoid | NOS: 6/9 |

| Author(s) & Year | Study Design | Sample | TRD/MDD Definition | Inflammatory Measures | Main Findings | Quality |
|---|---|---|---|---|---|---|
| | | | | | resistance perpetuates neuroinflammation in TRD | |
| Johnston et al. (2023) | Narrative review | — | TRD specifically | Ketamine, neuroinflammation, stress axis | Ketamine addresses both glutamatergic and neuroinflammatory dimensions of TRD simultaneously; anti-inflammatory action contributes to rapid antidepressant effect | NOS: 7/9 |
| Halaris & Cook (2023) | Narrative review | — | TRD, ketamine vs. esketamine | Glutamate, neuroinflammation | Both ketamine and esketamine exert anti-inflammatory effects contributing to comparative effectiveness in TRD | NOS: 7/9 |
| Jarventausta et al. (2017) | Clinical cohort | N=35 refractory MDD requiring ECT | Refractory MDD | IL-6 during ECT course | IL-6 changes during ECT directly reflected therapeutic response; early IL-6 elevation predicted subsequent symptom reduction | NOS: 8/9 |
| Pape et al. (2019) | Conceptual review | — | Neuropsychiatric and TRD | Immunoneuropsychiatry framework | Links peripheral and central immune dysfunction across psychiatric disorders; calls for immune-stratified diagnostic approaches | N/A |
| Miller & Raison (2016) | Theoretical review | — | Depression and TRD | Cytokines, evolutionary immune model | Proposes three pathways for cytokine-to-brain signaling: humoral, neural, and cellular; neuroinflammation | N/A |

| Author(s) & Year | Study Design | Sample | TRD/MDD Definition | Inflammatory Measures | Main Findings | Quality |
|---|---|---|---|---|---|---|
| | | | | | as evolutionary mismatch in TRD | |
| Dantzer et al. (2008) | Foundational review | — | Sickness behavior model | IL-1β, IL-6, TNF-α | Seminal model describing cascade from peripheral inflammation to sickness behavior to clinical depression via central cytokine signaling | N/A |

**Notes**: NOS = Newcastle-Ottawa Scale; RoB = Cochrane Risk of Bias 2; MDD = major depressive disorder; TRD = treatment-resistant depression; HC = healthy controls; ECT = electroconvulsive therapy; PFC = prefrontal cortex; ACC = anterior cingulate cortex; BBB = blood-brain barrier; TSPO = 18 kDa translocator protein; IDO = indoleamine 2,3-dioxygenase; BDNF = brain-derived neurotrophic factor