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Changes in inflammatory parameters and antioxidants and their impact on clinical symptoms, including cognitive functions, in patients with schizophrenia – scoping review

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Abstract

Introduction: Schizophrenia, a complex mental disorder, severely impacts both individuals and society. Emerging evidence points to neuroinflammation, cytokine dysregulation, oxidative stress, and antioxidant imbalances as key contributors to its pathophysiology. This review seeks to dissect the relationship between these factors and schizophrenia, assessing their roles as potential biomarkers and therapeutic targets.

Material and methods: A literature search of PubMed, Web of Science, and PsycINFO was performed. We used search terms including "schizophrenia", "cytokines", "antioxidants", and "inflammatory markers". Based on predetermined criteria, relevant articles were selected, and their data was extracted and analyzed. We specifically examined the associations between particular cytokines, antioxidants, and schizophrenia symptoms, with a focus on antioxidants' role in regulating oxidative stress, a component of schizophrenia's neuroinflammatory process. The impact of antipsychotic treatments on cytokine levels and oxidative stress was also evaluated.

Results: Our findings suggest that cytokine dysregulation and antioxidant imbalances are associated with various clinical features of schizophrenia. Furthermore, antipsychotic treatment may modulate these factors, potentially improving symptoms. Additionally, specific cytokines, oxidative stress markers, and antioxidants may serve as potential biomarkers and therapeutic targets.

Conclusions: Overall, our review provides a comprehensive analysis of the links between inflammatory cytokines, antioxidants, and schizophrenia, thereby deepening our understanding of this disorder's pathophysiology and treatment strategies.

schizophrenia; immunology; cytokines; antioxidants

1. INTRODUCTION

Schizophrenia is a complex psychiatric disorder featuring cognitive, behavioral, and emotional symptoms, traditionally categorized into positive symptoms (among others hallucinations, delusions, disorganized thinking), negative symptoms (among others affective flattening, avolition, social withdrawal), and cognitive deficits

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(among others impairments in memory, attention, and executive functioning). Current treatments focus on dopaminergic neurotransmission, yet emerging research suggests an important role for immune system alterations, specifically inflammatory cytokine dysregulation, in the development and progression of schizophrenia [1, 2].

Cognitive Impairments in Schizophrenia

Schizophrenia consistently manifests cognitive impairments, irrespective of the illness phase [3]. As noted by Emil Kraepelin in his first description of schizophrenia, cognitive deficits significantly hinder patient's functionality, affecting their work duties, social relationships, and daily independent tasks. Unidirectional and effective therapy is often challenging due to the numerous cognitive impairments presented by patients [4, 5]. Cognitive deficits typically involve slowed intellectual activities, impaired memory, disrupted attention, reasoning, and difficulties in recognizing others' emotions [4]. Neuroimaging studies highlight a link between these cognitive impairments and enlargement of brain ventricles [6], spurring investigations into structural and functional brain changes in schizophrenia [7]. Predominantly affecting the frontal and temporal lobes, cognitive dysfunctions often manifest as attention and learning disorders, slowed perception of stimuli, and deterioration of fluid and verbal memory [3].

Immune Factors and Their Importance in Schizophrenia

Cytokines, small proteins produced by various cells, mediate and regulate immune responses. Alterations in the levels of pro-inflammatory and anti-inflammatory cytokines are linked to several neuropsychiatric disorders, including schizophrenia. Additionally, changes in cytokine levels have been associated with the severity of clinical symptoms and the response to antipsychotic treatment [8, 9, 10]. Inflammatory states in the body can affect the brain's functioning, impacting mood, cognitive functions, and behavior [11]. In schizophrenia pathogenesis, cytokines play a significant role as intermediaries between the nervous and immune systems. They modify neurotransmitter metabolism, affecting nerve cell function, and the ability to regulate synaptic transmission and neuroplasticity [8]. Studies describe diverse levels of Th1 and Th2 cytokines in schizophrenic patients [11, 12]. The way cytokine level changes influence schizophrenia symptoms remains a topic of active research [13].

In the 1960s, scientists identified atypical lymphocytes called P cells in schizophrenic patients' blood [14]. Further studies confirmed the presence of these cells [15]. Recent findings implicate chemokines in the immune system and neuroinflammation in schizophrenia [16]. Ermakov et al. (2023) identified genetic associations of chemokine and chemokine receptor gene polymorphisms in schizophrenia, suggesting chemokines play a role in the disorder's neurobiological processes [16]. Emerging research investigates the relationship between inflammatory cytokines and schizophrenia aspects like symptom severity, cognitive deficits, and mood alterations. Studies have also explored how antipsychotic treatment impacts cytokine levels and their potential as biomarkers for treatment response. However, these studies have inconsistent findings due to methodological differences, small sample sizes, or population heterogeneity. The literature suggests prenatal exposure to pathogens can affect schizophrenia development in the child due to the action of cytokines that can pass from the infected mother's body through the placenta. These cytokines participate in both the inflammatory response and CNS functioning, contributing to schizophrenia's cognitive deficits [11]. Patlola et al. (2023) found an inverse relationship between cognitive performance and systemic proinflammatory biomarkers, suggesting cognitive deficits reflect elevated proinflammatory biomarkers and highlight the importance of understanding the pathways between inflammation and cognitive decline in schizophrenia [17].

The role of oxidative stress in schizophrenia has been explored in recent studies [18]. Flatow et al. (2013) demonstrated a strong association between oxidative stress and schizophrenia, suggesting it could contribute to the disorder's pathophysiology [18]. Dietrich-Muszalska et

al. (2015) found schizophrenia patients showed more oxidative DNA damage than healthy individuals [19]. Sudasinghe et al. (2017) linked oxidative stress and inflammation in schizophrenia, focusing on biomarkers like nitric oxide, C-reactive protein, and lipid peroxidation [20].

This review aims to synthesize the existing literature on the associations between inflammatory cytokines and antioxidants and schizophrenia, particularly focusing on their relationships with clinical symptoms, cognitive deficits, and mood changes. Additionally, we examine the effects of antipsychotic treatment on cytokine levels. By understanding the role of cytokines and antioxidants in schizophrenia, this review may contribute to novel therapeutic strategies and potential biomarkers for diagnosis, prognosis, and treatment response.

2. MATERIALS AND METHODS

A literature review was performed using databases like PubMed, Scopus, PsycINFO, and Web of Science, since October 2021 up to May 2023. The search involved terms related to schizophrenia and inflammatory cytokines or antioxidants [1-4]. Each database was searched individually to account for unique indexing terms.

Eligibility Criteria:

Inclusion criteria included original research articles, human studies, articles in English, and studies reporting cytokine and antioxidant levels in blood, serum, or plasma in relation to schizophrenia and antipsychotic treatment [5-7].

Exclusion criteria comprised of conference abstracts, editorials, case reports, and studies lacking data on cytokines, antioxidants, or schizophrenia symptoms.

Data Synthesis:

A narrative synthesis summarized the study findings, with a meta-analysis not performed due to heterogeneity across studies. The results were organized based on cytokine type, clinical schizophrenia aspects, and antipsychotic treatment impacts on cytokines and antioxidants [8, 9].

Selection process:

The initial search identified 319 articles. After title and abstract screening, 63 articles met the inclusion criteria. The rest were excluded for reasons such as ineligible design, insufficient data.

3.RESULTS

3.1 Interleukin 6 in schizophrenia

Interleukin 6 (IL-6) is an inflammatory marker that has been repeatedly connected to schizophrenia. A series of studies [21, 22, 23] has underlined the heightened presence of IL-6 in patients suffering from schizophrenia. This cytokine, primarily produced by macrophages, neurons, and microglial cells, is an integral part of the body's immune response, triggering B cells to produce antibodies [24]. Elevated levels of IL-6 often correlate with the emergence of psychotic disorders and are even observed under stressful circumstances.

A particular study involving 25 patients with first-episode schizophrenia showed an increase in IL-6 levels in their blood serum, which later reduced after treatment [25]. In a different study conducted by Lin et al. (1998) [26], they examined the blood serum of 27 schizophrenia patients, noting an increase in IL-6 levels irrespective of treatment status. A significant difference was observed in the levels of IL-6 in patients resistant to treatment when compared to those responding to treatment and healthy individuals. The study also reported decreased CC16 protein levels in patients, a protein known for its anti-inflammatory activity [26].

In a research study carried out by Stojanovic et al. (2014) [27], they measured IL-6 serum levels in patients showing prodromal symptoms of psychosis, patients with psychotic disorders, and healthy volunteers. The findings were significant, as patients with prodromal symptoms and patients with psychotic disorders showed higher levels of IL-6 than the control group. The researchers concluded that IL-6 levels were strongly associated with the occurrence of schizophrenia's negative symptoms. The results also indicated that elevated IL-6 levels were related to positive symptoms in patients with prodromal symptoms. The study proposed that IL-6

could serve as a potential marker for early psychotic symptoms [27].

3.2 Interleukin 1β in schizophrenia

Interleukin 1β (IL-1β) is a cytokine produced by microglial cells and astrocytes, and its presence can be identified in the bloodstream or cerebrospinal fluid [11]. Increased IL-1β levels in the cerebrospinal fluid of infected patients can lead to changes in mood and behavior, such as reduced pleasure, cognitive dysfunction, and social withdrawal [28]. Injecting IL-1β into rats led to changes in dopamine, an essential neurotransmitter for emotional responses and higher mental functions [29]. Söderlund's study (2009) [30] reported elevated IL-1β concentration in the cerebrospinal fluid of first-episode schizophrenia patients, which indicated the potential role of cytokines in central nervous system inflammation. On the other hand, Kowalski's study (2001) [31] provided evidence of increased IL-1β and TNF-α levels in patients with acute paranoid schizophrenia, which returned to control levels post-antipsychotic treatment.

3.3 Tumor necrosis factor α in schizophrenia

Tumor necrosis factor α (TNF-α), another pro-inflammatory cytokine, is associated with the hypothalamus-pituitary-adrenal stress axis activation [25]. Its level rises in response to specific cell types like Th1 and Th17 [25]. Certain studies have reported a correlation between TNF-α levels and conditions such as sleepiness and anorexia [32]. Apart from its impact on neuroplasticity and immunity, TNF-α also influences neuronal survival [33].

Lv's study (2015) [34] involved 89 chronic schizophrenia patients and 43 healthy volunteers. Their blood was drawn to determine TNF-α levels, and the results showed that TNF-α was significantly higher in patients than controls, particularly those with cognitive dysfunction. Interestingly, post-antipsychotic treatment, TNF-α levels dropped. This decrease in TNF-α level correlated with an improvement in patients' cognitive function [34]. Another study by Na i Kim (2007) [21] indicated that TNF-α levels were higher in acute schizophrenia patients and returned to control levels after effective antipsychotic treatment. The study concluded that TNF-α might serve as a biomarker for acute schizophrenia and suggested that reducing TNF-α levels might be a novel approach to improving cognitive function [21].

3.4 Interleukin 8 in schizophrenia

Interleukin 8 (IL-8), a chemokine, has been indicated in several diseases, including schizophrenia [35]. Its primary function is to attract neutrophils to the site of inflammation. A study by Maes et al. (2002) [36] reported elevated IL-8 levels in resistant to treatment and treated schizophrenia patients, also in the other study it was observed in patients with paranoid schizophrenia [37]. An investigation by Brown et al. (2004) [38] linked elevated IL-8 levels to an increased risk of developing schizophrenia spectrum disorder in children later in life. The study further implied that inflammation could be a potential risk factor in the onset of psychotic disorders [38].

3.5 Interleukin 10 in schizophrenia

Interleukin 10 (IL-10) is an anti-inflammatory cytokine that is also associated with various central nervous system (CNS) diseases [39]. IL-10 primarily inhibits the release of pro-inflammatory cytokines by suppressing the activity of Th1 cells [39]. A study by Xiu et al. (2014) [12] reported reduced IL-10 levels in patients with first-episode schizophrenia, who represented increased cognitive deficits. However, a study by Kunz et al. (2011) [33] reported increased IL-10 levels in stable, treated patients. Such conflicting results indicate that IL-10 levels might be involved in schizophrenia psychopathology, but the exact relationship is yet to be fully understood [12]. The role of cytokines in psychiatric disorders, such as schizophrenia, is gaining more attention, and further research is necessary to understand their precise influence on disease onset, progression, and treatment response

3.6 Interleukin 12 in Schizophrenia

Interleukin-12 (IL-12), a cytokine originating from antigen-presenting cells (APCs), macrophages, monocytes, and dendritic cells, plays a crucial role in immune responses. Primarily active during intracellular pathogen invasion, IL-12 enhances the activity of key immune cells, including dendritic cells, macrophages, natural killer cells, and promotes IFN-γ secretion [40]. Evidence linking IL-12 to schizophrenia has been demonstrated by Bedrossian's study (2016) [41], where increased IL-12p40 was observed in the serum of 63 clozapine-treated patients. Similarly, Ozbey's study (2008) [42] demonstrated an association between a heterozygous state in the IL-12B (p40) region and schizophrenia predisposition, suggesting a potential genetic linkage.

3.7 Antipsychotic Treatment and Cytokine Levels

Changes in cytokine levels often accompany antipsychotic drug treatments. Notably, studies by Na and Kim (2007) [21] and Kim (2004) [43] showed a decrease in IL-6, TNF-α, IFN-γ, and TGF-β1 levels in patients' serum post-treatment with neuroleptics. Similar results were found by Kubistova (2012) [25], linking a decrease in IL-6 levels and reduced PANSS scores, a positive treatment outcome, to antipsychotic treatment.

In patients with chronic schizophrenia, after 28 days of treatment with aripiprazole, a decrease in the level of pro-inflammatory cytokines was observed, among others IL-1β, IL-6, TNF-α, IL-12, as well as increase in the level of anti-inflammatory cytokine such as IL-10. Patients also obtained reduced scores on the PANSS scale [44]. Another research, which included 26 patients with a diagnosis of schizophrenia and 26 healthy controls, aimed to measured the concentration of selected cytokines in the serum before and after 40 days of treatment with risperidone or clozapine. The results showed a decrease in the level of TNF-α and an increase in the level of IL-10 in the serum of patients with schizophrenia after neuroleptic treatment [45]. A study by Noto et al. (2014) [46] report increased IL-6, IL-10 and TNF-α levels in drug-naïve patients with the first-episode of psychosis compared to healthy controls. After 10 weeks of risperidone treatment, they observed a decrease in the levels of IL-6, IL-10, TNF-α and IL-4, compared to the levels before treatment. Antipsychotic treatment has anti-inflammatory effects, restoring the balance of immunological parameters [47].

3.8 Inflammatory Parameters Changes in Schizophrenia Patients

Various inflammatory parameters change in the blood of schizophrenia patients, summarized in Table 1. Table 2 elaborates on changes in immune system activity.

Table 1 Changes in selected inflammatory parameters in the blood of patients suffering from schizophrenia.

Parameter	Growth in schizophrenia	Decline in schizophrenia	No changes from the control group
IL-1β	Kowalski et al, 2001 [29]		Erbağci et al, 2001 [30]
IL-6	Na i Kim, 2007 [21] Ganguli et al, 1994 [22] Dunjic-Kostic et al,2013 [23] Kubistova et al, 2012 [25] Lin et al, 1998 [26] Zhang et al, 2002 [33] Kamińska et al, 2001 [35] Kunz et al, 2011 [31] Stojanovic et al, 2014 [27]		Erbağci et al, 2001 [30]

IL-8	Zhang et al, 2002 [33] Kamińska et al, 2001 [35] Maes et al, 2002 [34]		Erbağci et al, 2001 [30] Kubistova et al, 2012 [25]
IL-10	Kunz et al, 2011 [31] Maes et al, 2002 [34]	Kamińska et al, 2001 [35] Xiu et al, 2014 [12]	Kubistova et al, 2012 [25]
IL-12	Bedrossian et al, 2016 [39]		
TNF-α	Na i Kim, 2007 [21] Kubistova et al, 2012 [25] Kowalski et al, 2001 [29]	Lv et al, 2015 [32] Dunjic-Kostic et al, 2013 [23]	Erbağci et al, 2001 [30] Kunz et al, 2011 [31]

Table 2 Changes in the activity of the immune system in patients with schizophrenia.

Source	Study group	Investigated parameters of inflammation	Changes in parameters in schizophrenia.
Wójciak et al, 2012 [14]	32 patients in exacerbation and remission 32 healthy	sIL-2R, IL-4, IL-6 (serum)	During exacerbation of the disease: – increased number of CD19+ lymphocytes – increased level of sIL-2R cytokine – increased IL-4 (compared to remission and control group)
Hirata-Hibi i Hayashi, 1993 [15]	12 patients 5 healthy	Blood count	Presence of atypical P cells
Na i Kim, 2007 [21]	43 patients with acute psychotic symptoms (untreated) 50 healthy	IL-2, IL-4, IL-6, TNF-α, IFN-γ (serum)	Before antipsychotic treatment: – increase in the level of IL-6, TNF-α – decrease in the level of IL-2, IL-4, IFN-γ After 6 weeks of antipsychotic treatment: – decrease in the level of IL-6, TNF-α – IL-2, IL-4, IFN-γ levels unchanged
Kim et al, 2004 [41]	88 patients 88 healthy	IFN-γ (Th1) IL-4 (Th2) TGF-β1 (Th3) (blood plasma)	On admission to the hospital: – increase in the level of IFN-γ, TGF-β1 – decrease in the level of IL-4; After 8 weeks of treatment with neuroleptics: – increase in the level of IL-4 – IFN-γ, TGF-β1 normal
Ganguli et al, 1994 [22]	128 patients (including 24 never treated) 110 healthy	IL-6 (serum)	Increase in the level of IL-6
Dunjic-Kostic et al, 2013 [23]	43 patients in exacerbation and remission 29 healthy	IL-6, TNF-α (serum)	Increase in the level of IL-6 Decrease in the level of TNF-α in both exacerbation and remission of schizophrenia

Kubistova et al, 2012 [25]	25 patients with first episode 25 healthy	IL-6, IL-8, IL-10, TNF-α (blood plasma)	First Episode: – increase in the level of IL-6, TNF-α After 4 weeks of treatment with neuroleptics: – decrease in the level of IL-6 – no changes in TNF-α (no changes in IL-8, IL-10)
Erbağci et al, 2001 [30]	34 untreated patients with acute exacerbation 23 healthy	IL-1β, sIL-2R IL-6, IL-8, TNF-α (serum)	No changes in IL-1β, sIL-2R, IL-6, IL-8, TNF-α
Söderlund et al, 2009 [28]	26 men with first episode of schizophrenia 30 healthy	IL-1β, IL-6, IL-8, IL-2, IL-4, IL-5, IL-10, IFN-γ, TNF-α (CSF)	CSF cytokine levels: Increase in thelevelofIL-1β No change or low level of other parameters
Lin et al, 1998 [26]	27 patients (15 resistant to treatment; 12 non-resistant) 15 healthy	CC16 protein, IL-6, sIL-6R, gp130 (serum)	Increase in the level of IL-6, sIL-6R Decrease in the level of CC16
Kowalski et al, 2001 [29]	20 patients with exacerbation of paranoid schizophrenia 26 healthy	IL-1β, TNF-α (peripheral blood monocytes)	Exacerbation of paranoid schizophrenia: – increase in thelevelofIL-1β, TNF-α After treatment with neuroleptics: – decrease in thelevelofIL-1β, TNF-α to control levels
Zhang et al, 2002 [33]	70 patients resistant to treatment (weaned from neuroleptics) 30 healthy	IL-2, IL-6, IL-8 (serum)	Increase in the level of IL-2, IL-6, IL-8
Kamińska et al, 2001 [35]	24 patients with paranoid schizophrenia 28 healthy	IL-6, IL-8, IFN-γ, IL-10 IL-2, IL-4 (serum)	Increase in the level of IL-6, IL-8, IFN-γ Decrease in the level of IL-10 (no changes in IL-2, IL-4)
Kunz et al, 2011 [31]	53 stable, treated patients 80 healthy	IL-6, IL-10, TNF-α (serum)	Increase in the level of IL-6, IL-10 (no change in TNF-α)
Maes et al, 2002 [34]	31 patients(17 resistant to treatment and 14 treated) 7 healthy	IL-8, IL-10 (serum)	Increase in the level of IL-8, IL-10 (resistant to treatment and treated)
Bedrossian et al, 2016 [39]	63 treated patients 60 healthy	IL-12p40 (serum)	Increase in the level of IL-12p40
Ozbey et al, 2008 [40]	100 patients 116 healthy	IL-12B (p40)	Heterozygotes of the polymorphism have a higher probability of developing the disease

Kim et al, 2000 [9]	25 men in acute psychosis (untreated) 25 healthy	IL-1β, IL-2, IL-6 (blood plasma)	Acute psychosis: Increase in the level of IL-2 (no change in the level of IL-1β, IL-6) After 2 months of neuroleptic treatment: Decrease in the level of IL-2 (no change in the level of IL-1β, IL-6)
Stojanovic et al, 2014 [27]	17 patients with psychotic prodromal symptoms 77 patients with psychotic disorder 25 healthy	IL-6 (serum)	Increase in the level of IL-6 in patients with prodromal symptoms and psychotic disorders
Xiu et al, 2014 [12]	128 untreated with first episode 62 healthy	IL-10 (serum)	Decrease in the level of IL-10
Lv et al, 2015 [32]	89 treated patients 43 healthy	TNF-α (serum)	Decrease in the level of TNF-α
Brown et al, 2004 [36]	59 patients 105 healthy	IL-8, IL-1β, IL-6,TNF-α (serum)	Increase in the level of IL-8 (no change in the level of IL-1β, IL-6, TNF-α)

3.9 Antioxidants in Schizophrenia

Research has consistently linked oxidative stress and impaired antioxidant defenses with schizophrenia. Zhang et al. (2012) [48] identified an inverse correlation between total antioxidant status (TAS) and cognitive deficits. Maes et al. (2020) [49] and Sokolova et al. (2020) [50] further expanded this knowledge, establishing oxidative stress's role in differentiating various schizophrenia and Alzheimer's disease states. Li et al. (2021) [51] suggested a link between antioxidant defenses and treatment response in first-episode schizophrenia patients. A similar connection with antioxidant enzymes and weight gain following risperidone treatment was identified by Liu et al. (2022) [52].

Asevedo et al. (2013) [53] analyzed serum levels of chemokines, BDNF and oxidative markers in schizophrenia patients and healthy controls, and looked for the impact of these parameters on cognitive functions. Comparison of the level of oxidative stress markers in schizophrenia patients, treated and untreated, with the level of these parameters in healthy ones, was also carried out by Bai et al. (2018) [54].

Hong et al. (2017) [55] tested the concentrations of selected chemokines in patients with schizophrenia and in the control group, and assessed the Chemokine Index (CI), which takes into account markers that differ most between patients and healthy ones. Martínez-Cengotitabengoa et al. (2012) [56] determined the levels of oxidative stress markers in the blood of patients with first-episode psychosis, and explored the connections between oxidative stress markers and cognitive functioning after half a year of therapy.

A meta-analysis by Yang et al. (2023) [57] showed changes in the oxidative stress markers after antipsychotic treatment in patients with schizophrenia. The authors informed among others about the decrease in the activity of glutathione peroxidase (GPx) and in the level of malondialdehyde (MDA) in patients' blood. Results of studies collectively contributing to our understanding of the role of oxidative stress and impaired antioxidant defenses in schizophrenia, highlighting their potential as therapeutic targets and predictors of treatment response, are presented in Table 3.

Table 3 The results of the reported research.

Source	Study Group	Investigated Parameters	Changes of parameters in schizophrenia
Zhang et al. (2012) [42]	296 chronic schizophrenia patients and 181 healthy controls	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and plasma total antioxidant status (TAS)	– Lower TAS levels in patients than controls – Lower cognitive scores on the RBANS and nearly all of its five subscales in patients – TAS inversely associated with some domains of cognitive deficits in schizophrenia, such as Attention and Immediate Memory
Maes et al. (2020) [43]	40 patients with deficit schizophrenia, 40 patients with non-deficit schizophrenia, 40 healthy controls	OSTOX biomarkers and ANTIOX defenses, including lipid hydroperoxides (LOOH), malondialdehyde (MDA), advanced oxidation protein products (AOPP), sulfhydryl (-SH) groups, paraoxonase 1 (PON1) activity and PON1 Q192R genotypes, and total radical – trapping antioxidant parameter (TRAP)	– Deficit schizophrenia characterized by increased AOPP levels, and lowered – SH and PON1 activity – No changes in OSTOX/ANTIOX biomarkers in non-deficit schizophrenia – Increased OSTOX/ANTIOX ratio significantly associated with deficit schizophrenia
Li et al. (2021) [45]	354 Antipsychotic-Naive First-Episode (ANFE) Schizophrenia patients and 152 healthy controls	Plasma activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) enzyme, total antioxidant status (TAS), and malondialdehyde (MDA) levels	– Higher SOD, CAT, TAS levels but lower MDA levels and GPx activity than controls – GPx activity decreased in both responders and non-responders to risperidone after treatment – GPx activity decreased less and was higher in responders than in non-responders at follow-up
Sokolova et al. (2020) [44]	33 patients with paranoid schizophrenia, 18 patients with Alzheimer's disease	Antioxidant profile of blood plasma	– No significant systemic oxidative stress in both groups – "Thiol" oxidative stress present in both groups, more pronounced in treatment – responsive schizophrenia – Certain antipsychotics showed antioxidant properties
Liu et al. (2022) [46]	225 Antipsychotic-Naive First-Episode (ANFE) Schizophrenia patients and 125 healthy controls	Activities of plasma superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), level of malondialdehyde (MDA)	– Higher SOD and CAT activities but lower MDA levels and GPx activity than controls – CAT activity associated with body weight or BMI – SOD activity increased in the weight gain group after risperidone treatment – MDA level decreased in the non-weight gain group after treatment – Baseline SOD and GPx activities were predictors of weight gain at 12-week follow-up

Więdłocha et al. (2023) [50]	82 schizophrenia inpatients	Oxidative stress parameters and brain-derived neurotrophic factor (BDNF)	– MDA, N-formylkynurenine (N-formKYN), AOPP, AGE, and total oxidative status (TOS) levels related to the PANSS-total score – MDA, reduced glutathione (GSH) and BDNF levels related to the PANSS – negative score – TOS and kynurenine (KYN) levels related to the PANSS – positive score – Levels of total antioxidant status (TAS) and AOPP along with the CDSS score related to the BACS-total score – TAS and N-formKYN levels related to the BACS-working memory score
Asevedo et al. (2013) [53]	30 Schizophrenia patients and 27 healthy controls	BDNF, TBARS, protein carbonyl content (PCC) and the chemokines CXCL-10/IP-10, CXCL-8/IL-8, CCL-11, CCL-24/ Eotaxin-2, CCL-2/MCP-1, CCL-3/MIP-1	-higher levels of BDNF and the chemokine CCL-11 in patients than controls -lower levels of TBARS and the chemokine CXCL-10/IP-10 in patients than controls In schizophrenia patients: – positively correlations between the levels of BDNF and semantic generation tasks, -negatively correlations of protein carbonyl content with working memory ability, -negatively correlations of CCL-11 and working memory test results, -positively correlations of CCL-11 and cognitive flexibility task, -positively correlations of CXCL-8/IL-8 with verbal fluency test results, -positively correlations of CCL-24/Eotaxin-2 with semantic generation ability and letter memory task
Bai et al. (2018) [54]	80 schizophrenia patients (40 first-episode, drug-free; 40 chronically medicated) and 80 healthy controls	Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), total antioxidant capacity (T-AOC), malondialdehyde (MDA) in serum	-lower activity of serum GSH-Px in unmedicated schizophrenics in compared to healthy ones -higher activity of serum GSH-Px, higher MDA levels, lower activity of SOD in chronically medicated patients -lower activity of SOD during short-term antipsychotic treatments
Hong et al. (2017) [55]	134 outpatients with schizophrenia or schizoaffective disorder and 112 healthy controls	11 chemokines in plasma: MCP-1 (CCL2), MIP-1α (CCL3), MIP-1β (CCL4), Eotaxin-1 (CCL11), MCP-4 (CCL13), TARC (CCL17), MDC (CCL22), Eotaxin-3 (CCL26), IL-8 (CXCL8), IP-10 (CXCL10), fractalkine (CX3CL1)	– higher levels of MCP-1, MIP-1β, Eotaxin-1, TARC, MDC in schizophrenics in compared to healthy ones -higher chemokine index in older patients, with protracted duration of the disease, with more negative symptoms

Martínez-Cengotitabengoa et al. (2012) [56]	28 first-episode psychosis patients and 28 healthy controls	Total antioxidant status, superoxide dismutase (SOD), total glutathione (GSH), catalase (CAT), glutathione peroxidase, lipid peroxidation, nitrites, the chemokine monocyte chemoattractant protein-1 (MCP-1)	– lower levels of total antioxidant status, catalase and glutathione peroxidase in patient's blood – negatively correlations of levels of MCP-1 and cognitive functions like learning and memory, – negatively correlations of levels of nitrite and executive function, – positively correlations of levels of glutathione and executive function

4. DISCUSSION

In this comprehensive review, we explored the role of fluctuating inflammatory cytokine levels, oxidative stress, and impaired antioxidant defenses in schizophrenia's pathophysiology. The findings demonstrate that these elements play a significant part in the disease manifestation and progression, potentially providing clues towards better diagnosis and treatment strategies. The association between the levels of inflammatory cytokines and schizophrenia's symptoms has been established in several studies [9]. These biomarkers might help understand shifts in patients' cognitive functioning. For instance, Miller's meta-analysis (2011) [10] identified IL-6 as an indicator of schizophrenia exacerbation, which normalizes post-antipsychotic treatment. This highlights a correlation between the degree of schizophrenia's worsening and cytokine levels. In stable outpatients, IL-6 blood levels equated those of control groups, while patients with first-episode psychosis or acute relapse exhibited higher IL-6 levels in their blood serum [10]. Several studies emphasize the relationship between cytokine levels and the manifestation of positive symptoms in schizophrenia patients [13]. However, research by Griffiths et al. (2023) [58] and Sæther et al. (2023) [59] indicate that neuroinflammation might not be the central feature of schizophrenia. Instead, they propose a blend of genetic and immune-neurodevelopmental dysregulation. These studies also link cognitive impairment with innate immune dysregulation in some individuals with severe mental illness [58,59].

Certain studies aimed at examining cytokine levels in schizophrenic patients who had discontinued medication for a minimum of two weeks, comparing these levels with a control group [35]. These investigations confirmed that schizophrenic patients had elevated cytokine levels, thus reinforcing the existence of immune system disturbances in these individuals [35].

Changes in inflammatory parameters, like IL-6 and TNF-α, occur regardless of whether the patient is in relapse or remission from schizophrenia [23]. The process of immune activation in schizophrenia's course has been confirmed by a meta-analysis that included 62 studies [60]. The investigation showed increased IL-1 RA, sIL-2R, and IL-6 levels in the peripheral blood of patients with schizophrenia and decreased in vitro IL-2 levels.

Furthermore, research indicates that an increase in IL-6 levels in the blood may indicate a worsening of schizophrenia symptoms [10, 27]. Similar relationships were identified with TNF-α [21,31], IL-1β [31], IL-8 [10,35,36], and a decrease in IL-10 levels [10,37]. These changes in cytokine levels are associated with schizophrenia exacerbation.

Several studies examined the relationships between various interleukins and schizophrenia symptoms or risk factors. They investigated the association between IL-6 and the emergence of psychotic disorders [25,27] and negative symptoms [9, 27], between TNF-α and cognitive deficits [34], IL-1β and mood or behavioral changes, including cognitive dysfunction [30], and IL-8 and the risk of developing a spectrum disorder of schizophrenia in children [38]. Additionally, they studied the link between decreased IL-10 levels and increased negative symptoms, including cognitive deficits [12], and between IL-12 and susceptibility to schizophrenia [42].

Other studies explored the role of oxidative stress and impaired antioxidant defenses in

schizophrenia [48,49,50,51,52,61]. They emphasized the potential of these elements as therapeutic targets, predictors of treatment response, and indicators of symptom severity. Meta-analyses by Das et al. (2019) [62], Fraguas et al. (2019) [63], and Goh et al. (2022) [64] provided additional insights, such as a reduction in glutathione levels in the anterior cingulate cortex in schizophrenia [62], an increased pro-inflammatory and pro-oxidative status in first-episode psychosis [63], and a reduction in antioxidant enzyme levels in schizophrenia patients, which potentially improve upon antipsychotic treatment [64].

This scoping review has several practical implications for understanding, diagnosing, and treating schizophrenia. The correlations between specific cytokines, oxidative stress markers, and schizophrenia symptoms suggest that therapies modulating these elements could be beneficial. Future research should explore anti-inflammatory agents, immunomodulatory drugs, antioxidant supplements, or cytokine-targeting therapies as possible supplementary treatments for schizophrenia.

Identifying cytokines and oxidative stress markers consistently altered in schizophrenia may help develop diagnostic and prognostic biomarkers. These biomarkers could assist in early diagnosis, risk stratification, and prediction of treatment response, relapse, or symptom exacerbation. Longitudinal studies investigating cytokine profiles and oxidative stress markers during the prodromal phase could provide early detection and intervention insights.

Our review underlines the need for a more personalized treatment approach, given the diverse alterations in cytokines and oxidative stress levels in schizophrenia. Clinicians could potentially tailor pharmacological interventions to target specific immune and oxidative dysregulations, optimizing treatment efficacy and minimizing side effects. Assessing these parameters in individual patients and monitoring them during treatment might aid in evaluating treatment response and adjusting medication.

Finally, this review acknowledges several limitations, including heterogeneity in study designs and methodologies, lack of standardized measurements, publication bias, limited longitudinal and intervention studies, potential confounding factors, and limited generalizability. Even with these constraints, the conclusions drawn from this review should be interpreted carefully. Nonetheless, they provide valuable insights into the relationships between inflammatory cytokines, oxidative stress, impaired antioxidant defenses, and schizophrenia, highlighting the need for further research to clarify these elements' roles in the disorder's pathophysiology.

5. CONCLUSIONS

In conclusion, our analysis provides a comprehensive overview of the current state of knowledge regarding the potential role of inflammatory cytokines, oxidative stress, and impaired antioxidant defenses in the pathophysiology of schizophrenia and their impact on clinical symptoms, including cognitive functions. The evidence presented suggests that cytokines such as IL-6, TNF-α, IL-1β, and IL-8, along with elements of oxidative stress and antioxidant defense, may be involved in the development and progression of the disorder. Moreover, the findings also indicate that treatment with antipsychotic medication can lead to changes in cytokine levels, oxidative stress markers, and improvements in symptom severity. These findings provide a significant contribution to the growing body of literature on the relationships between inflammation, oxidative stress, impaired antioxidant defenses, and schizophrenia, highlighting the potential of these elements as biomarkers and therapeutic targets. Further research in this area is needed to better understand the underlying mechanisms of cytokine dysregulation, oxidative stress, and impaired antioxidant defenses in schizophrenia, and to develop more effective treatments for this debilitating disorder.

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