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From Oxidative Stress to Immune Modulation: Targeting TLR, NLR, and MAPK Pathways with Probiotics in Schizophrenia

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Abstract: ***While existing reviews have broadly addressed the gut–brain axis in schizophrenia, the specific roles of oxidative stress, inflammation, and immune signaling cascades are rarely examined in an integrated manner. This review adopts a pathway-centered perspective to bridge that gap. Emerging evidence suggests that probiotics can ameliorate schizophrenia symptoms by counteracting oxidative stress, reducing systemic inflammation, and restoring immune homeostasis. We delineate how these three pathological layers are sequentially linked—oxidative damage triggering inflammation, which in turn drives innate and adaptive immune overactivation—and highlight TLR, NLR, and MAPK signaling as key molecular targets of probiotic intervention. Clinical studies, though still limited, indicate that adjunctive probiotics may lower serum inflammatory markers and improve psychiatric outcomes. We further discuss the implications for individualized strain selection and the integration of probiotics into multimodal treatment frameworks. By providing a mechanistic scaffold for the immunomodulatory effects of probiotics, this review aims to inform future translational research and precision probiotic strategies in schizophrenia.***

Keywords: Probiotics; Schizophrenia; Oxidative Stress; Inflammation; Immune Regulation; TLR/NLR/MAPK Pathways; Gut-Brain Axis; Adjunctive Therapy.

1. INTRODUCTION

Schizophrenia is a severe psychiatric disorder with a multifactorial etiology involving genetic, environmental, and biological factors [1,2]. A plethora of studies has unearthed numerous genetic susceptibilities specific to individuals with schizophrenia [2]. For example, the gene DRD2 is purported to have associations with irregular dopamine signalling, triggering the onset of the affliction [3]. Although current antipsychotic medications are effective for positive symptoms, they are often associated with significant metabolic side effects and limited efficacy against negative and cognitive symptoms. These shortcomings have fueled interest in novel therapeutic strategies targeting the gut–brain axis.

In recent years, the gut-brain axis has emerged as a key bidirectional communication network linking the central nervous system and the gut through neural, hormonal, and immune pathways [4]. Dysbiosis of the gut microbiota has been implicated in schizophrenia, and microbiota-based interventions—including probiotics, prebiotics, and fecal microbiota transplantation—offer new avenues to address both central symptoms and systemic comorbidities. Among these, probiotics have received particular attention for their anti-inflammatory properties, immunomodulatory capacity, and potential to influence schizophrenia-related pathophysiology [5,6].

In this narrative review, we focus on the interplay between oxidative stress, inflammation, and immune dysregulation in schizophrenia, and we evaluate how probiotics may modulate these pathways via TLR, NLR, and MAPK signaling. We also highlight the clinical evidence supporting probiotics as an adjunctive treatment and discuss future directions for personalized strategies.

To minimize selection bias, a systematic literature search was conducted in PubMed, Web of Science, and CNKI using combinations of the terms “probiotics”, “schizophrenia”, “gut-brain axis”, “oxidative stress”, “inflammation”, and “immune regulation”. References of retrieved articles were also screened. Studies published up to the end of 2024 were considered.

2. OXIDATIVE STRESS AND THE BASIS FOR PROBIOTIC INTERVENTION

2.1 The Role of Oxidative Stress in the Pathogenesis of Schizophrenia

In recent years, numerous studies have indicated the crucial role of oxidative stress in the etiology of schizophrenia [7]. Oxidative stress is the result of excessive accumulation of reactive oxygen species (ROS) within the body, leading to biomolecular damage, often related to an imbalance in the body's antioxidative defense system [8]. Research has found that, compared to healthy individuals, patients with schizophrenia have lower antioxidant enzyme activity and antioxidant content, which may be associated with increased oxidative stress [9]. A series of studies have confirmed changes in various biological oxidative stress parameters in blood samples from schizophrenia patients [10].

Studies have shown that oxidative stress is closely related to symptom manifestation in different stages of schizophrenia. In a study on acute-phase schizophrenia patients, it was found that their serum levels of malondialdehyde (MDA), hydrogen peroxide enzymes, and nitric oxide were significantly increased, while levels of fatty acyl hydrazide [11], superoxide dismutase [12], and glutathione were decreased. Furthermore, oxidative stress factor levels positively correlated with the severity of schizophrenia symptoms. An increasing number of studies have emphasized the importance of inositol and its metabolic products in neuroprotection and oxidative stress regulation [13]. These parameters may provide new clues for revealing the role of oxidative stress in the pathological biology of schizophrenia.

2.2 Mechanisms of Probiotics in Counteracting Oxidative Stress

Probiotics contribute to the regulation of oxidative stress through various mechanisms. Initially, probiotics can influence the gut microbiota composition, enhance gut permeability, and decrease the generation of endotoxins and inflammatory factors [14,15]. This aspect is particularly vital for schizophrenia patients, as the imbalance in their gut microbiota is intimately associated with the disease's etiology [16]. Furthermore, an improved gut repair function could reduce the oxidative stress response [17]. Probiotics may also directly neutralize free radicals and reactive oxygen species (ROS) responsible for oxidative stress. Some probiotics are capable of producing antioxidant enzymes like glutathione peroxidase and catalase to eliminate ROS [18,19]. Lastly, probiotics could modulate oxidative stress by impacting primary neurotransmitters, such as dopamine, glutamate, and gamma-aminobutyric acid [20]. These neurotransmitters are crucial in the development of schizophrenia symptoms, allowing probiotics to potentially alleviate some symptoms in schizophrenia patients to a certain extent [21].

2.3 Identification of Effective Strains and Products

Recent studies have indicated that probiotics can alleviate oxidative stress via various mechanisms. Initially, probiotics enhance the balance in the gut microbiota, subsequently reducing the generation of endotoxins and pro-inflammatory cytokines [22]. In a double-blind, placebo-controlled trial involving volunteers, it was discovered that *Lactobacillus rhamnosus* lessened intestinal permeability and decreased endotoxin and C-reactive protein levels, thus validating the effectiveness of probiotics in countering oxidative stress [17]. Additionally, probiotics indirectly modulate oxidative stress by enhancing the function of the intestinal barrier [23].

Probiotics can also combat oxidative stress by augmenting the activity of antioxidant enzymes. For instance, it has been observed that supplementation with *Bifidobacterium longum* results in amplified activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the mouse intestine, thereby boosting antioxidant capabilities [24].

3. INFLAMMATORY RESPONSE: THE CORE TARGET OF PROBIOTICS IN SCHIZOPHRENIA TREATMENT

3.1 Association Between Schizophrenia and Inflammation

In contemporary research, a multitude of studies have begun to expose a potential association between schizophrenia and systemic inflammation. It has been noted that the inflammatory response in individuals with schizophrenia is significantly elevated [25]. Some research indicates that relative to the general healthy population, individuals with schizophrenia have markedly increased levels of inflammatory indicators, such as Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and C-Reactive Protein (CRP) [26]. These pro-inflammatory cytokines could potentially contribute to the pathogenesis of schizophrenia through various pathways, encompassing abnormal neurodevelopment and disruptions in neurotransmitter metabolism [27].

Inflammatory responses could potentially be integral to the progression of schizophrenia. For instance, maternal infections during gestation can trigger neuro-inflammatory responses in the foetus, thereby increasing the likelihood of schizophrenia [28]. Further, individuals with active schizophrenia frequently demonstrate chronic low-level inflammation, which may intensify symptoms [29]. As such, mitigating inflammatory states in individuals with schizophrenia could represent a strategic approach to enhance the effectiveness of treatment.

3.2 Therapeutic Strategies for Modulating Inflammatory Responses with Probiotics

The influence of probiotics on inflammatory responses primarily manifests at the cellular and molecular levels. To begin with, probiotics enhance gut barrier mechanisms by modifying the gut microbial community, limiting the possibility of endotoxin Lipopolysaccharides (LPS) breaching the gut lining, which correspondingly lowers systemic inflammation [30]. Additionally, probiotics can modulate immune cell functions and the pathways for anti-inflammatory signals by producing short-chain fatty acids (SCFAs) like butyrate and acetate [20]. These SCFAs can restrain the actions of the NF-κB and MAPK signaling pathways, consequently curbing the creation of inflammatory elements such as IL-6, IL-1β, and TNF-α [31].

Specific variants like *Lactobacillus*, *Bifidobacterium*, and *Clostridium* are known to either directly or indirectly orchestrate inflammatory responses [32]. Lactobacilli carry immunoregulatory impacts capable of diminishing Th17 induced inflammatory reactions [33]. Bifidobacterium, notably *B. breve* and *B. longum*, generate copious amounts of acetate and stimulate gut epithelial cells to secrete the anti-inflammatory agent IL-10 [34]. Likewise, some bacterial metabolites, such as butyrate and propionate, have displayed their anti-inflammatory characteristics [35].

Although contemporary studies emphasize the potential of probiotics in managing inflammation, there still is a need for additional research to pinpoint anti-inflammatory probiotic strains and their clinical utilization. Forthcoming investigations should concentrate on: 1) strain specificity and individual variability, i.e., understanding how different strains and individuals vary concerning their anti-inflammatory impacts; 2) evaluating the effects of probiotics on the cellular and molecular processes behind mental disorders from a gut-brain axis perspective; 3) utilizing animal models and clinical tests to verify the impacts of various probiotic strains [36,22,37].

3.3 Theoretical Mechanisms of Symptom Relief through Inflammatory Regulation by Probiotics

Recent observations have shown increased serum inflammatory markers in schizophrenia patients, potentially indicating a substantial link to the disease's initiation and progression [38]. Probiotics, advantageous gut bacteria known to regulate inflammatory responses, have illustrated potential in treating various diseases, including digestive and cardiovascular diseases [39,40].

In terms of schizophrenia, probiotics may influence the disease's inflammation mechanisms in a plethora of ways, subsequently enhancing clinical symptoms. Initially, probiotics can regulate inflammation indirectly by promoting intestinal barrier functions. Research has indicated that an increase in gut permeability is commonly associated with schizophrenia, and utilizing probiotics to strengthen gut barrier function can alleviate the recurrent stimulation of endotoxins, thus reducing systemic inflammation [41,42].

Secondly, the probiotic intake can result in altering the composition of gut microbiota, steering it towards an inflammation-resistant condition. Probiotic variants such as *Lactobacillus* and *Bifidobacterium* generate short-chain fatty acids (such as butyrate, acetate, etc.), inhibiting the overactivation of Th17 cells in the gut and preventing a systemic inflammatory response, which escalates the risk of schizophrenia. The incorporation of specific probiotics could offer a more targeted approach to combat inflammation [43,44].

Finally, certain probiotics have the ability to directly affect neuroinflammation associated with schizophrenia. Substantially, strains like *Lactobacillus plantarum* can curtail the production of pro-inflammatory cytokines such as TNF-α, IL-6 in neurons and glial cells, inflammation markers closely tied to the worsening of schizophrenia [40,45].

3.4 Clinical Evidence and Personalized Treatment Strategies

Despite the limited availability of empirical research, emerging clinical studies have provided support for

employing probiotics in addressing inflammation in schizophrenia therapy. For instance, in a 2019 clinical trial, patients receiving 10 billion CFU of *Lactobacillus rhamnosus* and *Bifidobacterium animalis* experienced a significant decline in PANSS scores concurrently with a decrease in serum IL-6 and CRP inflammation indices [46]. Additionally, a study comparing conventional therapy with probiotic augmentation reported better improvements in inflammation markers, such as kynurenine and hsCRP, in the probiotic group versus the control group [47].

Though current laboratory and clinical research has not provided definitive guidance on the specific types and dosage of probiotics, the future may allow for the selection of probiotics for schizophrenia management based on individual patient requirements. For example, determining the optimal type and dosage of probiotics tailored to a patient's unique inflammatory response and disease stage could become feasible. Utilizing emerging technologies, such as gene-editing tools, future research may potentially develop more customized probiotic strains, paving the way for personalized treatment addressing the inflammatory mechanisms of schizophrenia [22,48].

4. MOLECULAR MECHANISMS OF PROBIOTICS IN MODULATING IMMUNE SIGNALING PATHWAYS

4.1 TLR Signaling Pathway

Probiotics, which consist of beneficial microorganisms, are crucial for sustaining gut equilibrium, enhancing digestion, absorption, and regulating immune functions [49]. They function primarily by interacting with toll-like receptors (TLRs) [50], essential immune system pathways for pathogen recognition, clearance, and the regulation of cell growth and cytokine production [51]. Probiotics typically modulate the host's immune response by interacting with both the host's pathogens and TLRs present on cell surfaces and within the endoplasmic reticulum [52].

TLRs exhibit specific distribution patterns, with certain TLRs like TLR2 and TLR4 situated on intestinal epithelial cells where they govern cytokine release and pathogen detection [53]. Research has demonstrated that probiotics can impact the host's immune function via TLR binding. For instance, when bound to TLR2, probiotics can mitigate the endoplasmic reticulum stress response, exerting anti-inflammatory effects [54]. Similarly, when probiotics interact with TLR4, they induce macrophages to produce antimicrobial peptides and anti-inflammatory factors, augmenting resistance to pathogens [55].

Specific probiotic metabolites, such as short-chain fatty acids (SCFAs) and polysaccharides, can selectively bind to and activate TLR signaling pathways, thereby modulating immune functionality [56]. For example, SCFAs can alleviate intestinal inflammation by stimulating the TLR2 signaling pathway [57]. In a similar vein, probiotic polysaccharides can boost macrophages' activation capabilities by engaging the TLR4 signaling pathway, which in turn enhances the clearance of dead cells [58].

4.2 NLR Signaling Pathway

In addition to modulating immune function through Toll-like receptors (TLRs) signaling pathways, probiotics can also impact NLRs signaling pathways [59]. NLRs are predominantly found in the cytoplasm and play a role in detecting intracellular pathogenic factors, as well as in regulating inflammatory responses and cell apoptosis [60].

Probiotics can stimulate the activation of inflammasomes, such as NLRP3, via interaction with NLRs signaling pathways [61]. Research has indicated that probiotics like *Bifidobacterium* and *Lactobacillus* can regulate inflammatory responses and activate caspase-1 through the NLRP3 inflammasome, subsequently generating inflammation factors IL-1β and IL-18 [62]. Furthermore, autophagy in cells can be activated by probiotics like *Bifidobacterium* through NLRP6 and NLRP12 signaling pathways, resulting in anti-inflammatory effects [63].

Probiotic metabolites, including short-chain fatty acids (SCFAs), can also influence immune function. For instance, butyrate and valerate can elevate IL-1β production through the activation of the NLRP3 inflammasome, potentially reducing or moderating the severity of diseases [64]. Moreover, probiotic-derived polysaccharides, via interaction with NLRs like NOD2, can aid in alleviating intestinal inflammation and ameliorating symptoms of inflammatory bowel diseases (IBD) [65].

Additionally, probiotics can affect the development of regulatory T cells (Tregs) through NLRs signaling

pathways [66]. Studies have demonstrated a positive association between probiotics administration and an increase in the number of Tregs and the production of anti-inflammatory factors. Probiotic interaction with NLRP2 fosters an increase in Tregs numbers, resulting in a decline in the inflammatory response, thus significantly improving disease conditions [67].

4.3 MAPK Signaling Pathway

MAPK signaling pathways have critical roles in molecular events associated with immune regulation [68]. Probiotics influence these functions by interacting with intestinal epithelial cells, leading to the production of transforming growth factor TGF-β1 in dendritic cells (DCs). This interaction inhibits Th1 and Th2 differentiation, while promoting T cell formation [69,70]. These effects are accomplished by acting on the ERK1/2 and p38 sites in impaired MAPK pathways [71]. Furthermore, probiotics can generate a substance called the serine protease functional domain, which preserves the intestinal mucosal barrier function by inhibiting the activation of the MAPK signaling pathway [72].

Additionally, probiotic metabolites, such as short-chain fatty acids (SCFAs), can interact with DCs, thereby inhibiting multiple inflammatory mediators like TNF-α, NO, and increasing TGF-β1 secretion [31]. These impacts are achieved through SCFAs interaction with G protein-coupled receptors (GPCRs) on the cell membrane, subsequently down-regulating the activity of p38, JNK, and NF-κB, which in turn enhance the immune phenotype [73,74].

5. MULTI-PATHWAY INTEGRATION: THE IMMUNOMODULATORY POTENTIAL OF PROBIOTICS IN SCHIZOPHRENIA

5.1 Synergistic Regulation of Oxidative Stress and Inflammation

Schizophrenia is a multifaceted mental disorder encompassing various factors, including genetics, the environment, and neurobiology [75]. Recent research indicates that probiotics have the ability to modulate the immune system, potentially improving oxidative stress and inflammatory responses [76].

Oxidative stress and inflammation are key contributors to the development and progression of schizophrenia [77]. Studies have shown altered levels of oxidative stress-related biomarkers in the serum of schizophrenic patients, such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [78]. Moreover, abnormal levels of inflammatory cytokines, including IL-2, IL-1β, and TNF-α, have been identified in the serum of schizophrenic patients [79]. Consequently, targeting oxidative stress and inflammation pathways may offer a novel strategy for alleviating schizophrenia symptoms.

Probiotics can counteract external pathogens, repair the intestinal barrier, reduce intestinal permeability, and mitigate oxidative stress through mechanisms involving glutathione regulation [80,81]. Additionally, probiotics can temper the inflammatory response by increasing the production of anti-inflammatory factors like IL-10 and TGF-β, as well as decreasing the secretion of pro-inflammatory cytokines such as IL-1β and TNF-α [82,83].

In conclusion, probiotics modulate inflammation and oxidative stress via the immune system [84]. This modulation is primarily evident in the enhancement of antigen presentation capability, the increased activity of natural killer cells, and the impact on T cell subset distribution [85,86]. The immunomodulatory effect of probiotics may hold potential therapeutic value in schizophrenia treatment through various interactions [87].

5.2 Therapeutic Prospects of Immunomodulation via TLR/NLR/MAPK Pathways

As research on schizophrenia advances, growing attention is given to the chronic low-grade inflammation and oxidative stress observed in patients with the disorder. Studies reveal that these conditions may lead to abnormally increased levels of substances such as inflammatory cytokines, nucleic acids, and oxidative stress products [28,7,88]. These alterations could potentially impact neurotrophins and even induce neuronal apoptosis, potentially contributing to the pathogenesis of schizophrenia [89].

Several investigations have demonstrated that probiotics can modulate the immune system, with significant implications stemming from their regulation of Toll-like receptors (TLRs), NOD-like receptors (NLRs), and the Mitogen-Activated Protein Kinase (MAPK) pathways [90]. Both TLRs and NLRs are part of the innate immunity

receptor family and are directly related to immune response and inflammatory reactions [91]. As a primary cellular response to environmental changes, the MAPK pathway regulates a multitude of cellular biological processes [92].

Probiotics have been shown to decrease inflammatory cytokines IL-1β, IL-6, and TNF-α levels in the blood of schizophrenic patients [93,94]. They recognize Pathogen Associated Molecular Patterns (PAMPs) through TLRs and NLRs receptors and activate related signaling pathways, directing immune cells to produce anti-inflammatory cytokines [95]. Furthermore, probiotics can modulate oxidative stress levels in patients with schizophrenia by inhibiting NF-κB and ERK/MAPK pathways [96], which is crucial for alleviating emotional and cognitive impairments in these patients [97].

Some probiotics may also promote neuronal growth and protect the blood-brain barrier's permeability via specific pathways. For example, probiotics such as *Lactobacillus* and *Bifidobacterium* can facilitate neurotrophic factor expression and neuronal growth and repair by managing TLR signaling and regulating NF-κB and MAPK pathways [4,98]. Additionally, they help maintain the blood-brain barrier's permeability, allowing the brain to defend against external harmful substances and providing protection [99].

In summary, probiotics could serve a role in schizophrenia treatment by regulating specific receptors and signaling pathways. This is evidenced by their ability to reduce inflammation, enhance oxidative stress levels, promote neuronal growth, and improve blood-brain barrier permeability. Despite these promising findings, the research in this area is still in its infancy, and more comprehensive studies are required to confirm the clinical effects of probiotics in the future.

6. CONCLUSION AND DISCUSSION

Emerging research shows the potential of probiotics to positively influence schizophrenia by modulating immune responses and mitigating oxidative stress [88]. Specifically, certain probiotics can decrease inflammatory cytokine levels and boost antioxidant enzyme activity, which may contribute to symptom alleviation [100]. Their non-pharmaceutical nature, high safety, and compatibility with existing medications make probiotics an attractive adjunct therapy [101,88]. Clinical studies further suggest that combined use with antipsychotics may improve patient outcomes and quality of life [102,103].

However, several obstacles remain. The long-term efficacy of probiotics is not yet defined, and their safety profiles require further clarification [104,105]. Optimal strains, dosages, and administration regimens have yet to be established [106]. Consequently, rigorous large-scale trials are needed to confirm effectiveness and guide personalized treatment strategies. Alongside clinical work, mechanistic studies should focus on key signaling pathways (e.g., TLR, NLR, MAPK) to identify molecular targets and provide a solid rationale for therapeutic applications [105].

In summary, while still in its early stages, probiotic-based intervention holds promise as a novel component of schizophrenia management. By deepening our understanding of the underlying immune-regulatory mechanisms, it may be possible to integrate probiotics into personalized, biologically informed treatment frameworks and ultimately improve clinical outcomes.

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