Review



# Gut-Brain Inflammation Due to Toxin-Activated Mast Cells and Microglia in Autism Spectrum Disorder

Pejman Katiraei , Richard E Frye , Theoharis C Theoharides *

Posted Date: 20 June 2025

doi: 10.20944/preprints202506.1715.v1

Keywords: brain; flavonoids; folinic acid; gut; inflammation; luteolin; mast cells; microbiome; microglia; toxins

 doi:10.20944/preprints202506.1715.v1



*Review*

# Gut-Brain Inflammation Due to Toxin-Activated Mast Cells and Microglia in Autism Spectrum Disorder

**Pejman Katiraei [1], Richard E. Frye [2] and Theoharis C. Theoharides [3,4,*]**

[1] Wholistic Kids and Families, Santa Monica, CA 90403, USA
[2] Autism Discovery and Treatment Foundation, Phoenix, AZ 85050, USA
[3] Institute for Neuro-Immune Medicine, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Ft. Lauderdale, FL 33328, USA
[4] Laboratory of Molecular Immunopharmacology and Drug Discovery, Department of Immunology, Tufts University School of Medicine, Boston, MA 02111, USA
* Correspondence: Institute for Neuro-Immune Medicine, Nova Southeastern University, 3400 Gulf to Bay Blvd, Room 3748, Clearwater, FL 33759, USA; Phone: (813) 574-5218; ttheohar@nova.edu or pkatiraei@gmail.com

**Abstract:** Recent data from the CDC indicate that the incidence of Autism Spectrum Disorder (ASD), a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors [1], has increased to 1 in 31 children. Individuals with ASD have a constellation of neurological, behavioral, sensory, feeding, gastrointestinal, and immunological issues. This manuscript discusses how these can be explained by disruption of the gut-blood and blood-brain barriers due to microbiome dysbiosis which then results in chronic endotoxemia leading to chronic cycle of gut-brain inflammation via mast cell and microglial activation. We present how various environmental, pathogenic and stress factors can disrupt the gut-brain homeostasis to create susceptibility and epigenetic effects contributing to the development of ASD. We also offer a safe, simple, and effective treatment approach to addressing some of the key pathogenetic underpinnings of ASD.

**Keywords:** brain; flavonoids; folinic acid; gut; inflammation; luteolin; mast cells; microbiome; microglia; toxins

## 1. Introduction

Autism Spectrum Disorder (ASD) is increasing at an alarming rate and now impacts 1 in 31 children in the United States [2], with a projected total cost of $461 billion by 2025 [3]. While genetic vulnerabilities are known to be a significant contributing factor to ASD, environmental factors, particularly environmental toxicants, may be another reason for the increased prevalence of ASD [4,5]. The microbiome and total gut physiology can also influence the onset of ASD and can be highly predictive of ASD [6].

Environmental toxins, including glyphosates, heavy metals, synthetic compounds and plastics, mold toxins, air pollution, COVID, and excessive use of antibiotics are just some examples of factors that can compromise gut permeability, induce gut-mediated inflammation, and disrupt the microbiomes [3,7–13]. Neonatal events such as C-section delivery and early use of antibiotics are also known to disrupt the microbiome [14] and may contribute to an increased risk of ASD [15–17]. What is not yet well understood is how transient, yet significant, exposures to environmental toxins and stressors contribute to ASD.

This paper discusses how such exposures disrupt the gut-brain axis leading to a chronic state of neuroinflammation primarily via activation of mast cells and microglial that can explain the physical,

 doi:10.20944/preprints202506.1715.v1



cognitive, psychological, and social findings in at least a subset of individuals with ASD. It further offers a simple, safe, and inexpensive set of recommendations to mitigate the inflammatory response and improve subjects with ASD.

## 2. Relevant Clinical Findings

Individuals with ASD have abnormal neuronal apoptosis [18], myelination [19] and neuroplasticity [20]. They also have dysfunction in multiple areas of cognition including: attention, executive functioning, working memory, praxis and motor planning [21]. Moreover, individuals with ASD experience significantly higher rates of anxiety [22], obsessive compulsive disorder (OCD) [23], social anxiety [24], abnormal perception of fear [25], anger and aggression [26]. This chronic state of psychological stress can trigger inflammation within the nervous system [27] and gastrointestinal tract [28]. These individuals also struggle with abnormalities in the processing of complex sensory information [29], with sensory processing disorders affecting up to 80-95% of individuals with ASD. The severity of these sensory processing disorders is a significant predictor of ASD severity and everyday functioning [30–32].

Children with ASD are also at a 500% higher risk of developing feeding problems [33], such as food selectivity, food refusal, and poor oral intake, as compared to neurodevelopmentally normal children [34,35]. Children with ASD have texture aversion and strong preferences for foods like carbohydrates and processed foods [36,37], and a higher risk of healthy food avoidance: vegetables (56% refusal), eggs (43%), fruits (42%), chicken (35%), and meat (24%) [35].

Individuals with ASD have a significantly higher prevalence of intestinal inflammation and inflammatory bowel disease [38] and are four times more likely to have gastrointestinal symptoms vs controls [36,39], including constipation (odds ratio 3.86), diarrhea (OR 3.63), abdominal pain (OR 2.45) [39], and these symptoms can begin as early as 6-18 months of age [40]. Individuals with ASD also have abnormal intestinal permeability [41], abnormal microbiomes [42] with a possible [43] higher prevalence of *candida* versus controls [44]. These individuals also have complex patterns of systemic immune dysregulation [45,46], with brain inflammation including microglia activation [47] and elevations of various cytokines in the cerebrospinal fluid [46,48], including the neuropilin disruptor matrix metalloproteinase-9 (MMP-9) [49]. The immune dysregulation also presents as higher rates of food allergies [50] and atopic diseases including asthma, allergies, and eczema, which are also strongly correlated with the risk of ASD50.

## 3. How Environmental Exposures Create Chronic Gastrointestinal Inflammation and Dysfunction

ASD is likely due to genetic vulnerabilities activated by to environmental toxins and stressors [51], with a significant contribution from the environmental factors themselves [52,53]. Some of these vulnerabilities occur at the gut level [54], including how host genetics interact with the gut microbes to shape the immune and metabolic state of ASD [55]. One such example is the role of the human leukocyte antigen (HLA) haplotypes, of which HLA haplotypes A2, DR4, and DR11 have been found to create major susceptibility for ASD45. These haplotypes can determine the specificity of T lymphocyte and natural killer (NK) cell responses, which then influence the makeup of the commensal bacteria [56].

As such, each individual has a genetically determined threshold of gut resilience and tolerance to various stressors or toxins. Thus, if an environmental factor or combination of factors supersede this threshold, the gastrointestinal tract and microbiome can become compromised setting off a complex cascade of gut-immune-brain dysregulation. At the center of this dysregulated axis are the gastrointestinal mast cells (Figure 1).

 doi:10.20944/preprints202506.1715.v1



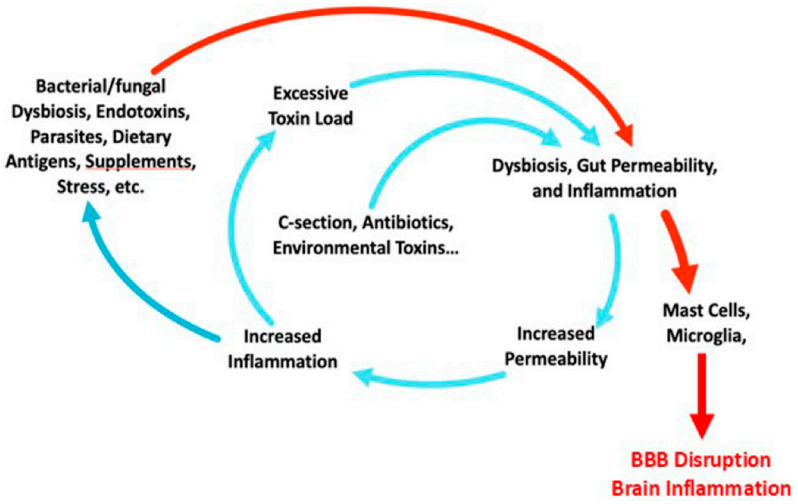


**Figure 1.**

## 4. The Role of Mast Cells in Chronic Gastrointestinal Inflammation

Mast cells are the sentinels of our immune system [57] and can be activated by many of the same triggers that disrupt the gut, including: heavy metals, herbicides (including glyphosates), polychlorinated biphenyl (PCB), lipopolysaccharides (LPS), mycotoxins and molds, as well as pathogens [58] including *Borrelia* [59,60], and *Helicobacter* pylori [61] (Figure 2). Once activated, they orchestrate complex arrays of immune activation including mediating the allergy response [62], a finding common in individuals with ASD.

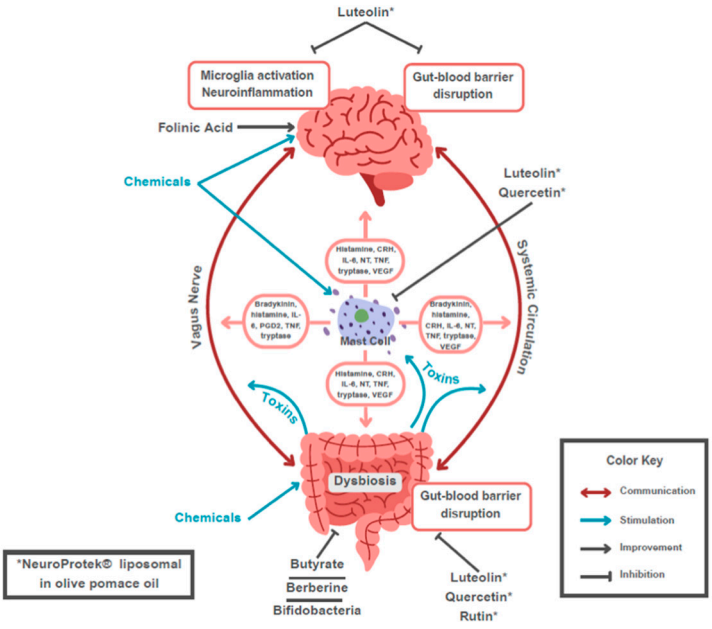


**Figure 2.**

The largest population of mast cells is in the gastrointestinal tract, where they play a fundamental role in maintaining the intestinal barrier by regulating epithelial function and integrity, managing the defensive and immuno-regulatory function, modulating both innate and adaptive mucosal immunity, and maintaining neuro-immune interactions. These functions all play a fundamental role in the health or disease of the gut [63,64].

 doi:10.20944/preprints202506.1715.v1



The gastrointestinal tract harbors trillions of bacteria, fungi (the mycobiome), viruses, LPS, and dietary antigens. The microbiota are well known to play an important role in neuropsychiatric disorders [65]. Separating this complex and potentially deadly "internal" gut content from our circulation and organ systems, including the brain, is a tightly regulated interface consisting of a mucus layer, immunoglobulin A, defensins, a single epithelial layer held together by tight junction proteins, and a carefully orchestrated immune surveillance in the lamina propria of the gut [66]. As long as this gut barrier is healthy and intact, and the bacterial and fungal communities are healthy, the likelihood of systemic and chronic inflammation is low. If there is a disruption in the microbial communities or gut barriers, the likelihood of a chronic systemic and nervous system inflammatory responses rise dramatically [67–70].

Zonulin and occludin are two important tight junction proteins that ensure the integrity of the intestinal barrier. Aberrant mast cell activation can cause profound disruption to the gut through damage to these tight junction proteins via mediators such as histamine, MMP-9, TNF-$\alpha$ and tryptase, resulting in increased intestinal permeability and inflammation, a critical step that allows the translocation of the commensal bacteria [63,66,71]. Through the release of numerous mediators mast cells can further diminish the integrity of the gut barrier, sensitize dendritic cells to microbial signals, including LPS, and influence the behavior of the innate and adaptive immune response [72–74]. Small intestinal mucosal damage may decrease the activity of diamine oxidase (DAO) [75], a key enzyme that degrades histamine, and thus exacerbate the detrimental effects of histamine that is released by activated mast cells. Mast cells can directly and indirectly suppress the function of T regulatory cells, while simultaneously promoting the activation, recruitment, proliferation and cytokine secretion in multiple T-cell subsets [62].

These combined changes to the gastrointestinal tract barrier and microbiome are sufficient for the pathogenesis of food allergies [76]. Especially in young children, even minor changes to the barrier function early in life can lead to exposure to luminal antigens which can result in allergies in later stages of life [77], as found in individuals with ASD. These gut abnormalities can also explain the gastrointestinal symptoms found in individuals with ASD, including abdominal pain, constipation, and diarrhea [78–80].

Perhaps, the most significant consequence of this toxin-mediated gut dysfunction is how it influences the makeup of the microbiome. Abnormalities in T-cell activity directly impact microbial diversity [81]. Inflammation-mediated dysbiosis, an emerging concept where gut inflammation alters the intestine's oxidative and metabolic environment, can also profoundly influence the survival and growth of the gut bacteria and lead to a deviation of the commensal population from a healthy, diverse symbiotic profile to microbial communities with reduced complexity and over-representation of particular taxa of microbes [66,82].

Furthermore, certain toxins, like mycotoxins can alter the production of intestinal specific immunoglobulins [83], which then significantly influence the composition and behavior of the bacterial and fungal makeup of the microbiome [84–88]. Mast cell activation and the concurrent gut and microbiome disruptions can also induce *candida* species to switch from a harmless commensal to a virulent pathobiont, which is then able to invade tissues and disseminate in the body [71,89,90]. In turn, the invasive form of *candida,* and the toxin its hyphae form secretes, candidalysin [91], can trigger significant mast cell activation [92,93], thus creating a vicious cycle of chronic gut and immune dysfunction. Further complicating this picture, *candida* can alter the makeup of the microbiome through multiple mechanisms [94] and prevent the regrowth of *lactobacilli* after antibiotic treatment, while promoting the colonization of *enterococcus* [95]. All of these factors in turn perpetuate *candida*'s virulent pathobiont state. These mycobiome abnormalities also influence the maturation and priming of the immune system [96] and create an additional factor to induce or exacerbate the allergic state [97] that, as noted, is more prevalent in ASD [98].

These findings may explain the significant microbiome and mycobiome abnormalities found in individuals with ASD [99,100]. Because this dysbiosis is largely immune-mediated, it often responds poorly to conventional gut treatments, such as probiotics.

 doi:10.20944/preprints202506.1715.v1



## 5. Gut Disruption and Bacterial Translocation

The innate immune system within the gut has pattern recognition receptors (PRRs) whose primary purpose is to detect pathogens, including the commensal bacteria, by recognizing molecules and structures on the pathogens called pathogen-associated molecular patterns (PAMPs) [101]. The disruption of the gut barrier allows pathogenic commensal bacteria to breach the gut, at which point their PAMPs are recognized by the PRRs, which then activate the intestinal epithelial cells (IECs) to secrete cytokines and chemokines. This inflammatory reaction triggers a larger immune response to clean up the foreign and damaging antigens and threats, thus resulting in further inflammation and cytokine release [66]. These inflammatory cytokines further disrupt the epithelial barrier by downregulating tight junctions (claudin-1, occludin, zonula occludens protein-1) and adherens junctions (E-cadherin) in IECs [66]. One consequence of this pathogenic breach of the gut barrier and the ensuing inflammatory response becomes the key step in the induction and persistence of gut inflammation inflammatory bowel diseases [102], which is more prevalent in children with ASD versus healthy controls [103].

Another serious consequence of the compromised gut barrier is the entry of dangerous bacterial components into the systemic circulation. The gram-negative bacterial surface glycolipid lipopolysaccharide ( LPS), is among the most potent pro-inflammatory neurotoxins [104,105]. Gut dysbiosis and a disrupted gut barrier allow for the translocation of LPS through the gut lining into the systemic circulation to allow the development of a low-grade, chronic generalized toxin-associated effects [106], as is found in individuals with ASD [107]. The toxicity of the LPS increases with the degree of dysbiosis [105]. Numerous animal models suggest a strong link between generalized toxin effects and the features of ASD [108–111]. One study in rats reported autistic features after a single prenatal exposure to LPS [112]. Propionic acid is also known to cause similar effects [113,114].

Once absorbed, LPS can trigger systemic inflammation, with a reduction in T regulatory (Tregs) lymphocytes, increase in Th17 and Th1 lymphocytes, along with increased TNF-$\alpha$, NFkB, IL-6, IL-8, IL- 10, and IL-12 [105,115]. Children with ASD also have activation of inflammasome complexes, including the NLRP3 inflammasome [116], which are complex systems that play a critical role in the regulation and activation of the body's inflammatory response. LPS can rapidly prime and activate this inflammasome [117], which could be further primed by candidalysin [117,118]. Furthermore, within the intestinal lining, LPS binds to PRRs (TLR4) on intestinal cells [106] and mast cells [119,120], thus triggering additional inflammation within the gut and further disrupting the tight junction proteins and gut barrier.

The most concerning effect of LPS occurs within the nervous system. The microglia are the innate immune cells that modulate the inflammatory response within the central nervous system [46]. Peripheral gut inflammation and damage can activate the microglia [121–123]. In healthy adult volunteers, 1 ng/kg of LPS (similar levels found in some healthy adults) can trigger robust microglial activation in most areas of the brain as measured by PET within three hours of injection [115]. In rodents, a single intraperitoneal injection of 5 mg LPS/kg causes microglial activation that persists for at least 12 months [115]. Several other animal studies have also shown systemic LPS can activate the microglia [124–127]. If animals are given multiple doses of 1 mg LPS/kg (over several days), a model for chronic generalized toxin effects, they experience neuroinflammation, BBB permeability, and rapid neurodegeneration [115], findings that are common in individuals with ASD [128,129].

Even low levels of LPS can induce sickness behavior through elevation of inflammatory cytokines [115,130–132]. Sickness behavior, an adaptive change in behavior as a result of inflammation, has been described in individuals with ASD and can present as anxiety, appetite loss, depression, headache, impaired alertness and focus, lethargy, muscle pain, and social withdrawal [115,133].

The impact of LPS on the CNS is likely through multiple mechanisms, including the vagus nerve (Figure 2) [123]. LPS cannot pass through or directly disrupt the blood-brain barrier (BBB) [115]. On the other hand, central histamine, various toxins, a high fat, high sugar diet are just a few of the factors

 doi:10.20944/preprints202506.1715.v1



that can compromise the BBB [134–138], thus allowing LPS to directly enter with CNS. Stress via the release of corticotropin-releasing hormone CRH) can also disrupt the BBB through activation of mast cells [139–141].

Microglia shape neuronal plasticity and connectivity, and synaptic function and wiring through neuronal pruning [142–144]. They regulate myelin growth and integrity [145] and when activated may cause severe demyelination [146]. They are also involved in abnormal neuronal apoptosis [147]. By disrupting neuronal circuitry, microglial activation impairs the processing and integration of various sensory and emotional responses as part of the presentation of ASD [46,148,149]. Individuals with ASD have been found to have microglial activation [150], also confirmed through postmortem findings [151] and on functional positron emission tomography [152].

Microglial activation also alter the neuronal pathways of the amygdala, which has been shown to disrupt the fear threshold within human beings and may present as ASD [153]. Disruptions in the amygdala can also play a significant role in the pathogenesis of aggressive behavior [154], addictive behaviors [155,156], anxiety disorders [157], impulse control disorder [158], attention deficit disorder [159], depression, and a host of other neuropsychiatric findings [160]. These behavioral and psychiatric findings are all noted in individuals with ASD [161–165].

Furthermore, activated microglia may induce post-synaptic calcium elevation causing increased neuronal reactivity and disrupt glutamate signaling [144]. Microglia can also alter the levels of quinolinic acid [166], a potent neurotoxin implicated in ASD [167]. Microglial activation can also disrupt the behavior of the astrocytes [168], which in turn can further disrupt glutamate homeostasis, upset GABA regulation, and neuronal pruning [144].

Beyond the effects of the microglia, human and animal studies have shown that endotoxin-induced inflammation can also increase the neural responses in the anterior cingulate cortex and prefrontal regions further impacting the processing of social and emotional information [169]. Beyond the microglia are the mast cells, which serve as an “immune gate to the brain” and communicate with microglia in a two-way activation [170–173].

## 6. Mast Cells and ASD

Peripheral gut inflammation activates mast cells within the nervous system [174]. This is further impacted by psychological stress [175,176]. Mast cell activity is intimately tied to microglial activity, and the activation of one cell line can lead to the activation of other immune cells through multiple pathways (Figure 3) [168].

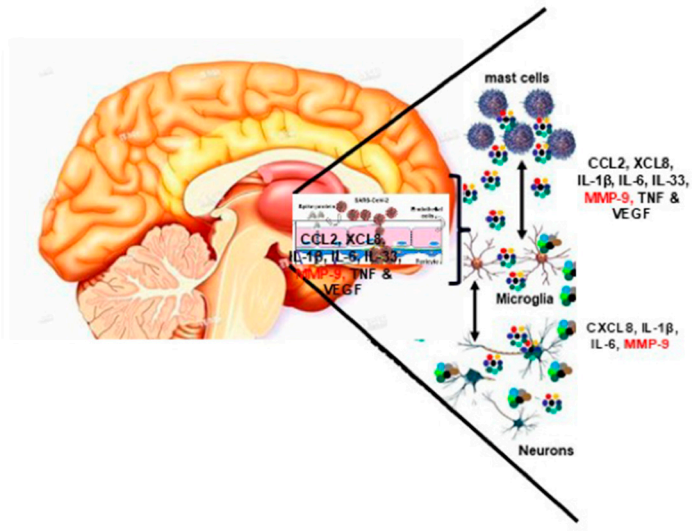


**Figure 3.**

 doi:10.20944/preprints202506.1715.v1



The role of mast cell and microglial activity has been well described by Theoharides, et al. in individuals with ASD [46,177–179]. Mast cell activity can disrupt the blood-brain barrier, and release multiple chemokines, cytokines, tissue disruptors and neurotoxic molecules, like IL-6 that create localized inflammation in the area of the basic ganglia that disrupts neuronal connectivity and contributes to ASD-related behaviors [180]. Mast cells also trigger a neuroinflammatory response through multiple mechanisms [46,47,181]. They can induce mitochondrial translocation to the cell surface with the secretion of extracellular mitochondrial adenosine triphosphate (ATP) and DNA that is then detected by the immune system as 'innate pathogens' triggering a significant inflammatory response, potentially contributing to ASD [182]. This mitochondrial DNA may also induce a neuro-inflammatory response, which has been found to alter behavior in mouse models [183]. Theoharides has suggested that this profound sequence of neuro-inflammatory response is sufficient to cause ASD in some [180].

Gut-mediated mast cell activation (and gut histamine) can increase histamine levels within the CNS, likely through multiple pathways, although the exact mechanisms are not yet clear [184]. It is clear that activated microglia and mast cells within the brain produce 50% of all brain histamine [185], and in animal models, intraperitoneal LPS injection can activate brain mast cells and cause a rapid elevation of central histamine within 6 hours [186].

Histamine plays a critical role in modulating the nervous system [187]. It regulates alertness and is also a key wake-promoting neurotransmitter that influences the circadian rhythm and sleep-wake behavior [185]. Sleep disruption is a common feature of ASD [188]. Elevated levels of central histamine can also disrupt the vestibular system, which is critical for balance, motor planning, and sensory perception [187]. Histamine has also been shown in animal models to directly or indirectly influence various sensory pathways: sound processing [189], tactile sensation [190], and olfactory perception [187,191]. The disruption of these sensory pathways may explain the host of sensory findings found in individuals with autism, including eating problems and food texture avoidance [192]. The intensity of sensory issues has been associated with more significant social difficulties, lower adaptive functioning, and lower or divergent visual exploration of social environments in children with ASD [193]. These sensory abnormalities are also strongly associated with social motivation and difficulties with initiating or maintaining social interactions, or feeling tense in social situations [193].

Furthermore, because of these sensory abnormalities and eating problems, individuals with ASD avoid fiber-rich vegetables and foods that are often rich in simple carbohydrates, fats, and sometimes highly processed foods [35,194]. These dietary preferences can exacerbate any microbiome disruption [195] and increase the abundance of *candida* [*196*]. The high amounts of carbohydrates and fats, and few dietary fibers can also dramatically enhance the absorption of LPS and induce an inflammatory response [197]. However, certain fruits and vegetable contain histamine (e.g. avocado, pineapple, spinach, tomatoes) that should best be avoided, especially in those with polymorphisms in the histamine degrading enzymes diamine oxidase (DAO) and histamine N-methyl transferase (HNMT). [198]

## 7. How to Address Gut-Brain Inflammation Effectively

While it is beyond the scope of this paper, numerous options are available to address many parts of this proposed cycle of physiological dysfunction and endogenous toxicity (Table 1).

Theoharides, et al. have demonstrated significant clinical improvements of symptoms in children with ASD from a dietary supplement which contains liposomal (formulated in olive pomace oil) luteolin (100 mg/softgel) quercetin (70 mg/softgel), and the quercetin glycoside rutin (30 mg/softgel)(NeuroProtek) [199–201]. The noted studies all suggest that these supplements are safe and well tolerated.

**Table 1.**

 doi:10.20944/preprints202506.1715.v1



**Basic Dietary Supplements for Autism Spectrum Disorders**

| Main Target | Products | Intended use |
|---|---|---|
| **Neuronal Health** | Folinic acid, calcium folinate = Leukovorin # | Can bypass dysfunctional folate receptors alpha; does not require MTHFR - best in the presence of mutations (C677T) |
| | 5-Methyfolate = 5-MTHF | A form of active folate |
| | S-Adenosylmethionine (SAMe) | Methyl donor, mood stabilizer |
| **Allergic Inflammation+** | Berberine | Antipathogenic, mast cell blocker |
| | Bifidobacterium infantis, B. lactis, B. longum | Reduces histamine, anti-inflammatory |
| | DAO (diamine oxidase)& | Degrades histamine |
| | Luteolin+Quercetin (Neuroprotek®) (liposomal in olive pomace oil) | Anti-oxidant. anti-allergic, anti-inflammatory, neuroprotective |
| | Methoxyluteolin (GentleDerm®) | Anti-allergic, anti-inflammatory, soothing |
| | Vitamin D3 | Immune regulator |
| **Oxidative Stress** | Glutathione | Anti-oxidant |
| | N-Acetyl cysteine (NAC) | Increases glutathione, anti-oxidant |

+ Use low casein, gluten, histamine, oxalate, salicylate diet
& Acid resistant or enteric-coated
# Prescription

The terahydroxyflavone luteolin is a well-studied bioflavonoid with a host of anti-inflammatory properties [202–204]. Luteolin has been found to inhibit mast cell and T cell activation [205], and decrease levels of histamine and TNF [206,207]. In fact, luteolin was recently shown to be a more potent inhibitor that the "mast cell stabilizer" drug cromolyn [208]. Luteolin can also enter the brain and reduce microglial activation [209], particularly as a result of LPS [210], as well as have antibacterial properties [211]. Pentaxydroxyflavonol quercetin can inhibit mast cells and is more effective than cromolyn at blocking mast cell cytokine release [212]. It can also balance the Th1/Th2 immune response [213], reduces gut permeability while improving microbial diversity [214], and protects against LPS-induced gut damage through multiple mechanisms [215]. Rutin is another important compound because of its ability to liberate quercetin in the gut. The delivery base is just as important, since olive pomace oil that not only increases absorption from the gut, but it offers the well-known cytoprotective properties of olive oil [216]. Unfortunately, many cheaper preparations of luteolin and quercetin in powder form have flooded the market but are either of low purity or the daily dose requires multiple capsules [217]. The common notion that if you take higher amounts of luteolin or quercetin in powder form will eventually allow some of the flavonoids to be absorbed is not only wrong but dangerous as the unabsorbed flavonoids accumulate in the gut and disrupt the microflora [218].

The structural luteolin analogue, tetramethoxyluteolin, is even more potent than luteolin in inhibiting both mast cells and microglia [219–223], and has been incorporated in the novel anti-allergic skin lotion (GentleDerm) [224], which is particularly useful in those individuals with both eczema and ASD.

 doi:10.20944/preprints202506.1715.v1



Two additional compounds that may play an useful role in the treatment of ASD are palmitoylethanolamide (PEA) and diamine oxidase (DAO) enzymes. PEA is a naturally occurring fatty acid amine found in soybean lecithin, egg yolk, and peanut meal. PEA has noticeable anti-inflammatory properties and can regulate mast cell activation [225–227] by reducing release of TNF-a and histamine [228]. Furthermore, PEA displays neuroprotective properties and can inhibit microglial activation [229], particularly as a result of LPS exposure [230]. In isolated case reports, PEA has been shown to be beneficial in ASD [230].

DAO enzymes are naturally occurring enzymes within the gastrointestinal tract that are responsible for the degradation of histamine within the gut. Since intestinal mucosal damage may decrease the DAO activity [75], additional supplementation may play an important role in normalizing histamine levels within the gut and reducing the inflammatory and possibly neurological findings. Histamine intolerance has also been associated with anxiety disorders [231]. Exogenous supplementation with DAO enzymes can significantly reduce histamine levels within the gastrointestinal tract and the signs and symptoms of histamine intolerance [232], including extra-intestinal symptoms such as headaches [233]. To our knowledge, DAO enzymes are safe and well tolerated. However, DAO preparations vary considerably in their stated activity and most the enzyme will be degraded by the stomach acidity unless they are in acid resistant formulations.

Addition of berberine, lactoferrin and Bifidobacteria infantis/longum could provide additional benefits as they all have both antibacterial and anti-inflammatory properties [234–239]. The combination of these naturally occurring compounds may prove useful in the treatment of ASD.

Addition of folinic acid (Calcium folinate, Leucovorin) has been shown to significantly improve brain health, cognition and language by bypassing surface folate receptors and the enzyme MTHFR, especially in those with anti-folate receptor antibodies and MTHFR polymorphisms (Table 1) [240].

There are obvious limitations to the suggested treatment approached discussed above. The clinical efficacy of these compounds may be limited in the face of significant gastrointestinal disease or serious environmental exposures, such as living in a home with severe mold contamination.

## 8. Beyond the Clinical Benefits

Unfortunately, at the time of this publication, there are few clinically available and reliable diagnostic tools that can help clinicians accurately assess these assessing gut-mediated pathophysiological events, including:

(1) Assessing candida and the mycobiome – There are many commercially available stool kits to assess the bacterial component of the microbiome. Unfortunately, these kits lack the sensitivity to accurately detect disturbances of candida or other fungal components of the microbiome (mycobiome).
(2) Assessing microglial activation – No commercially available diagnostic modalities are available to accurately assess microglial activation.
(3) Assessing mast cell activity and histamine – Serum histamine has a half-life of less than two minutes and thus cannot be used to accurately detect histamine imbalances. Serum tryptase can be used to assess significant mast cell burden (e.g. systemic mastocytosis), which may limit its ability to detect more subtle forms of mast cell activation, including within the central nervous system. Urinary N-methylhistamine, Prostaglandin F2 alpha and leukotrience E4 must be collected cold in 24-hour urine and most clinical labs do not perform them.
(4) Assessing endotoxemia – At this time there is no commercially available diagnostic tool available to directly assess endotoxemia.
(5) Assessing total toxin load – Currently, only specialty tests are available to assess select categories of toxins. These tests are not FDA-approved and their results are at times called into question.

These points demonstrate the profound limitations in our current diagnostic tools to detect these critical physiological processes in individuals with ASD. They also highlight how important future

 doi:10.20944/preprints202506.1715.v1



well-designed research studies are in helping us further our understanding of ASD, and to allow this science to be effectively utilized in the clinical setting.

## 9. Conclusion

There is no singular trigger, event, genetic or physiological process that is solely responsible for the onset of ASD in the majority of cases. It is the total load of pathogenic and environmental toxins, which varies from individual to individual, compounded by other infectious [241], microbiome/gut, physiological and psychological stressors that may be responsible for the onset of ASD in some individuals [242]. We believe that in these individuals, there is a moment during gestation/delivery, in infancy or early childhood where the gut barriers, microbiome and gut-mediated immune responses surpass a threshold of homeostasis, and enter into a perpetual cycle of neuroinflammation.

While there is sufficient data to identify the individual factors contributing to ASD risk, additional research is needed to bring this vast array of findings into one cohesive model that has the power to assess the unique exposome for each individual and appreciate the total physiological impact it can have, including on the mitochondria and other organ system dysfunctions that have been associated with ASD. Additional research is also needed to assess the role that bacterial endotoxins may play in the manifestation of ASD.

In the meantime, the proposed interventions can inhibit some of the pathogenetic pathways and allow the gut-brain axis to recover as has been the case in numerous individuals with ASD.

**Author Contributions:** Conceptualization and writing-original draft, P.K., writing contribution – review and editing, T.H. and R.F., visualization, T.H. and P.K..

**Disclosures:** TCT is the Scientific Director of Algonot LLC(Sarasota, FL) that formulates and markets unique dietary supplements.

## References

1. American Psychiatric Association 1994 Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. American Psychiatric Association, Washington, D.C
2. Shaw KA, Williams S, Patrick ME, Valencia-Prado M, Durkin MS, Howerton EM, Ladd-Acosta CM, Pas ET, Bakian AV, Bartholomew P, Nieves-Muñoz N, Sidwell K, Alford A, Bilder DA, DiRienzo M, Fitzgerald RT, Furnier SM, Hudson AE, Pokoski OM, Shea L, Tinker SC, Warren Z, Zahorodny W, Agosto-Rosa H, Anbar J, Chavez KY, Esler A, Forkner A, Grzybowski A, Agib AH, Hallas L, Lopez M, Magaña S, Nguyen RHN, Parker J, Pierce K, Protho T, Torres H, Vanegas SB, Vehorn A, Zhang M, Andrews J, Greer F, Hall-Lande J, McArthur D, Mitamura M, Montes AJ, Pettygrove S, Shenouda J, Skowyra C, Washington A, Maenner MJ. Prevalence and Early Identification of Autism Spectrum Disorder Among Children Aged 4 and 8 Years - Autism and developmental disabilities monitoring network, 16 sites, United States, 2022. *MMWR Surveill Summ. 2025, 74* (2), 1-22. DOI: 10.15585/mmwr.ss7402a1.
3. Chiu K, Warner G, Nowak RA, Flaws JA, Mei W. The Impact of environmental chemicals on the gut microbiome. *Toxicol Sci. 2020, 176* (2), 253-284. DOI: 10.1093/toxsci/kfaa065
4. Rossignol DA, Genuis SJ, Frye RE. Environmental toxicants and autism spectrum disorders: a systematic review. *Transl Psychiatry. 2014, 4* (2), e360. DOI: 10.1038/tp.2014.4
5. Chaste P, Leboyer M. Autism risk factors: genes, environment, and gene-environment interactions. *Dialogues Clin Neurosci. 2012, 14* (3), 281-92. DOI: 10.31887/DCNS.2012.14.3/pchaste
6. Su Q, Wong OWH, Lu W, Wan Y, Zhang L, Xu W, Li MKT, Liu C, Cheung CP, Ching JYL, Cheong PK, Leung TF, Chan S, Leung P, Chan FKL, Ng SC. Multikingdom and functional gut microbiota markers for autism spectrum disorder. *Nat Microbiol. 2024, 9* (9), 2344-2355. DOI: 10.1038/s41564-024-01739-1. Epub 2024, Erratum in: Nat Microbiol. 2025 Feb;10(2):600. doi: 10.1038/s41564-024-01900-w. PMID: 38977906
7. Tu P, Chi L, Bodnar W, Zhang Z, Gao B, Bian X, Stewart J, Fry R, Lu K. Gut microbiome toxicity: connecting the environment and gut microbiome-associated diseases. *Toxics. 2020, 8* (1), 19. DOI: 10.3390/toxics8010019

 doi:10.20944/preprints202506.1715.v1




8. Sondergaard TE, Fredborg M, Oppenhagen Christensen AM, Damsgaard SK, Kramer NF, Giese H, Sørensen JL. Fast screening of antibacterial compounds from fusaria. *Toxins (Basel). 2016, 8* (12), 355. DOI: 10.3390/toxins8120355.
9. Liew WP, Mohd-Redzwan S. Mycotoxin: Its impact on gut health and microbiota. *Front Cell Infect Microbiol. 2018, 8*:60. DOI: 10.3389/fcimb.2018.00060
10. Guerre P. Mycotoxin and gut microbiota interactions. *Toxins (Basel). 2020, 12* (12), 769. DOI: 10.3390/toxins12120769
11. Bernard-Raichon L, Venzon M, Klein J, Axelrad JE, Zhang C, Sullivan AP, Hussey GA, Casanovas-Massana A, Noval MG, Valero-Jimenez AM, Gago J, Putzel G, Pironti A, Wilder E; Yale IMPACT Research Team; Thorpe LE, Littman DR, Dittmann M, Stapleford KA, Shopsin B, Torres VJ, Ko AI, Iwasaki A, Cadwell K, Schluter J. Gut microbiome dysbiosis in antibiotic-treated COVID-19 patients is associated with microbial translocation and bacteremia. *Nat Commun. 2022, 13* (1), 5926. DOI: 10.1038/s41467-022-33395-6
12. Fouladi F, Bailey MJ, Patterson WB, Sioda M, Blakley IC, Fodor AA, Jones RB, Chen Z, Kim JS, Lurmann F, Martino C, Knight R, Gilliland FD, Alderete TL. Air pollution exposure is associated with the gut microbiome as revealed by shotgun metagenomic sequencing. *Environ Int. 2020,* 138:105604. DOI: 10.1016/j.envint.2020.105604
13. Mutlu EA, Comba IY, Cho T, Engen PA, Yazıcı C, Soberanes S, Hamanaka RB, Niğdelioğlu R, Meliton AY, Ghio AJ, Budinger GRS, Mutlu GM. Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome. *Environ Pollut. 2018,* 240:817-830. DOI: 10.1016/j.envpol.2018.04.130
14. Korpela K. Impact of delivery mode on infant gut microbiota. *Ann Nutr Metab. 2021,* 1-9. DOI: 10.1159/000518498
15. Nitschke AS, do Valle HA, Vallance BA, Bickford C, Ip A, Lanphear N, Lanphear B, Weikum W, Oberlander TF, Hanley GE. Association between prenatal antibiotic exposure and autism spectrum disorder among term births: A population-based cohort study. *Paediatr Perinat Epidemiol. 2023, 37* (6), 516-526. DOI: 10.1111/ppe.12972
16. Al-Zalabani AH, Al-Jabree AH, Zeidan ZA. Is cesarean section delivery associated with autism spectrum disorder? *Neurosciences (Riyadh). 2019, 24* (1), 11-15. DOI: 10.17712/nsj.2019.1.20180303
17. Hamad AF, Alessi-Severini S, Mahmud SM, Brownell M, Kuo IF. Early childhood antibiotics use and autism spectrum disorders: a population-based cohort study. *Int J Epidemiol. 2018, 47* (5), 1497-1506. DOI: 10.1093/ije/dyy162
18. Wei H, Alberts I, Li X. The apoptotic perspective of autism. *Int J Dev Neurosci. 2014,* 36:13-8. DOI: 10.1016/j.ijdevneu.2014.04.004
19. Galvez-Contreras AY, Zarate-Lopez D, Torres-Chavez AL, Gonzalez-Perez O. Role of oligodendrocytes and myelin in the pathophysiology of autism spectrum disorder. *Brain Sci. 2020, 10* (12), 951. DOI: 10.3390/brainsci10120951
20. Anashkina AA, Erlykina EI. Molecular mechanisms of aberrant neuroplasticity in autism spectrum disorders (Review). *Sovrem Tekhnologii Med. 2021, 13* (1), 78-91. DOI: 10.17691/stm2021.13.1.10
21. Zwick GP. Neuropsychological assessment in autism spectrum disorder and related conditions. *Dialogues Clin Neurosci. 2017 Dec, 19* (4), 373-379. DOI: 10.31887/DCNS.2017.19.4/gzwick
22. White SW, Oswald D, Ollendick T, Scahill L. Anxiety in children and adolescents with autism spectrum disorders. *Clin Psychol Rev. 2009, 29*(3), 216-29. DOI: 10.1016/j.cpr.2009.01.003
23. Meier SM, Petersen L, Schendel DE, Mattheisen M, Mortensen PB, Mors O. Obsessive-compulsive disorder and autism spectrum disorders: longitudinal and offspring risk. *PLoS One. 2015, 10* (11), e0141703. DOI: 10.1371/journal.pone.0141703
24. Montaser J, Umeano L, Pujari HP, Nasiri SMZ, Parisapogu A, Shah A, Khan S. Correlations between the development of social anxiety and individuals with autism spectrum disorder: a systematic review. *Cureus. 2023, 15* (9), e44841. DOI: 10.7759/cureus.44841
25. Mayes, SD, Calhoun, SL, Aggarwal, R, Baker, C, Mathapati, S, Molitoris, S & Mayes, RD. Unusual fears in children with autism. *Research in Autism Spectrum Disorders. 2013, 7* (1), 151-158. DOI: 10.1016/j.rasd.2012.08.002.

 doi:10.20944/preprints202506.1715.v1




26. Patel S, Day TN, Jones N, Mazefsky CA. Association between anger rumination and autism symptom severity, depression symptoms, aggression, and general dysregulation in adolescents with autism spectrum disorder. *Autism. 2017, 21* (2), 181-189. DOI: 10.1177/1362361316633566
27. Theoharides TC. Effect of stress on neuroimmune processes. *Clin Ther. 2020, 42* (6), 1007-1014. DOI: 10.1016/j.clinthera.2020.05.002
28. Katiraei P, Bultron G. Need for a comprehensive medical approach to the neuro-immuno-gastroenterology of irritable bowel syndrome. *World J Gastroenterol. 2011, 17* (23), 2791-800. DOI: 10.3748/wjg.v17.i23.2791
29. Leekam SR, Nieto C, Libby SJ, Wing L, Gould J. Describing the sensory abnormalities of children and adults with autism. *J Autism Dev Disord. 2007, 37* (5), 894-910. DOI: 10.1007/s10803-006-0218-7
30. Sanz-Cervera P, Pastor-Cerezuela G, Fernández-Andrés MI, Tárraga-Mínguez R. Sensory processing in children with autism spectrum disorder: relationship with non-verbal IQ, autism severity and attention deficit/hyperactivity disorder symptomatology. *Res Dev Disabil. 2015,* 45-46:188-201. DOI: 10.1016/j.ridd.2015.07.031
31. Tomchek SD, Dunn W. Sensory processing in children with and without autism: a comparative study using the short sensory profile. *Am J Occup Ther. 2007, 61* (2), 190-200. DOI: 10.5014/ajot.61.2.190
32. Suarez MA. Sensory processing in children with autism spectrum disorders and impact on functioning. *Pediatr Clin North Am. 2012, 59* (1), 203-14, xii-xiii. DOI: 10.1016/j.pcl.2011.10.012
33. Kanner L. Austic disturbances of affective contact. *Nervous Child. 1943,* 2:217–250.
34. Nadon G, Feldman DE, Dunn W, Gisel E. Association of sensory processing and eating problems in children with autism spectrum disorders. *Autism Res Treat. 2011,* 541926. DOI: 10.1155/2011/541926
35. Cherif L, Boudabous J, Khemekhem K, Mkawer S, Ayadi H, Moalla Y. Feeding problems in children with autism spectrum disorders. *Journal of Family Medicine. 2018, 1* (1), 30-39. DOI: 10.14302/issn.2640-690X.jfm-18-2252
36. Madra M, Ringel R, Margolis KG. Gastrointestinal issues and autism spectrum disorder. *Child Adolesc Psychiatr Clin N Am. 2020, 29* (3), 501-513. DOI: 10.1016/j.chc.2020.02.005
37. Baraskewich J, von Ranson KM, McCrimmon A, McMorris CA. Feeding and eating problems in children and adolescents with autism: A scoping review. *Autism. 2021, 25* (6), 1505-1519. DOI: 10.1177/1362361321995631
38. Kim JY, Choi MJ, Ha S, Hwang J, Koyanagi A, Dragioti E, Radua J, Smith L, Jacob L, Salazar de Pablo G, Lee SW, Yon DK, Thompson T, Cortese S, Lollo G, Liang CS, Chu CS, Fusar-Poli P, Cheon KA, Shin JI, Solmi M. Association between autism spectrum disorder and inflammatory bowel disease: A systematic review and meta-analysis. *Autism Res. 2022, 15* (2), 340-352. DOI: 10.1002/aur.2656
39. Wasilewska J, Klukowski M. Gastrointestinal symptoms and autism spectrum disorder: links and risks - a possible new overlap syndrome. *Pediatric Health Med Ther. 2015, 6*, 153-166.DOI: 10.2147/PHMT.S85717
40. Bresnahan M, Hornig M, Schultz AF, Gunnes N, Hirtz D, Lie KK, Magnus P, Reichborn-Kjennerud T, Roth C, Schjølberg S, Stoltenberg C, Surén P, Susser E, Lipkin WI. Association of maternal report of infant and toddler gastrointestinal symptoms with autism: evidence from a prospective birth cohort. *JAMA Psychiatry. 2015, 72* (5), 466-74. DOI: 10.1001/jamapsychiatry.2014.3034
41. de Magistris L, Familiari V, Pascotto A, Sapone A, Frolli A, Iardino P, Carteni M, De Rosa M, Francavilla R, Riegler G, Militerni R, Bravaccio C. Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. *J Pediatr Gastroenterol Nutr. 2010, 51* (4), 418-24. DOI: 10.1097 MPG.0b013e3181dcc4a5
42. Morton JT, Jin DM, Mills RH, Shao Y, Rahman G, McDonald D, Zhu Q, Balaban M, Jiang Y, Cantrell K, Gonzalez A, Carmel J, Frankiensztajn LM, Martin-Brevet S, Berding K, Needham BD, Zurita MF, David M, Averina OV, Kovtun AS, Noto A, Mussap M, Wang M, Frank DN, Li E, Zhou W, Fanos V, Danilenko VN, Wall DP, Cárdenas P, Baldeón ME, Jacquemont S, Koren O, Elliott E, Xavier RJ, Mazmanian SK, Knight R, Gilbert JA, Donovan SM, Lawley TD, Carpenter B, Bonneau R, Taroncher-Oldenburg G. Multi-level analysis of the gut-brain axis shows autism spectrum disorder-associated molecular and microbial profiles. *Nat Neurosci. 2023, 26* (7), 1208-1217. DOI: 10.1038/s41593-023-01361-0
43. Alookaran J, Liu Y, Auchtung TA, Tahanan A, Hessabi M, Asgarisabet P, Rahbar MH, Fatheree NY, Pearson DA, Mansour R, Van Arsdall MR, Navarro F, Rhoads JM. Fungi: friend or foe? a mycobiome

 doi:10.20944/preprints202506.1715.v1



evaluation in children with autism and gastrointestinal symptoms. *J Pediatr Gastroenterol Nutr. 2022, 74* (3), 377-382. DOI: 10.1097/MPG.0000000000003349

44. Li Q, Han Y, Dy ABC, Hagerman RJ. The gut microbiota and autism spectrum disorders. *Front Cell Neurosci. 2017,* 11:120. DOI: 10.3389/fncel.2017.00120
45. Robinson-Agramonte MLA, Noris García E, Fraga Guerra J, Vega Hurtado Y, Antonucci N, Semprún-Hernández N, Schultz S, Siniscalco D. Immune dysregulation in autism spectrum disorder: what do we know about It? *Int J Mol Sci. 2022, 23* (6), 3033. DOI: 10.3390/ijms23063033
46. Theoharides TC, Tsilioni I, Patel AB, Doyle R. Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. *Transl Psychiatry. 2016, 6* (6), e844. DOI: 10.1038/tp.2016.77
47. Theoharides TC, Asadi S, Patel AB. Focal brain inflammation and autism. *J Neuroinflammation. 2013,* 10:46. DOI: 10.1186/1742-2094-10-46
48. Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah I, Van de Water J. Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. *Brain Behav Immun. 2011, 25* (1), 40-5. DOI: 10.1016/j.bbi.2010.08.003
49. Rexrode LE, Hartley J, Showmaker KC, Challagundla L, Vandewege MW, Martin BE, Blair E, Bollavarapu R, Antonyraj RB, Hilton K, Gardiner A, Valeri J, Gisabella B, Garrett MR, Theoharides TC, Pantazopoulos H. Molecular profiling of the hippocampus of children with autism spectrum disorder. *Mol Psychiatry. 2024, 29* (7), 1968-1979. DOI: 10.1038/s41380-024-02441-8
50. Xu G, Snetselaar LG, Jing J, Liu B, Strathearn L, Bao W. Association of food allergy and other allergic conditions with autism spectrum disorder in children. *JAMA Netw Open. 2018, 1* (2), e180279. DOI: 10.1001/jamanetworkopen.2018.0279
51. Roe K. Autism spectrum disorder initiation by inflammation-facilitated neurotoxin transport. *Neurochem Res. 2022, 47* (5), 1150-1165. DOI: 10.1007/s11064-022-03527-x
52. Masini E, Loi E, Vega-Benedetti AF, Carta M, Doneddu G, Fadda R, Zavattari P. An overview of the main genetic, epigenetic and environmental factors involved in autism spectrum disorder focusing on synaptic activity. *Int J Mol Sci. 2020, 21* (21), 8290. DOI: 10.3390/ijms21218290
53. Serkan Y, Beyazit U, Ayhan AB. Mycotoxin exposure and autism: a systematic review of the molecular mechanism. *Curr Mol Pharmacol. 2021, 14* (5), 853-859. DOI: 10.2174/1874467213999200819145942
54. Niesler B, Rappold GA. Emerging evidence for gene mutations driving both brain and gut dysfunction in autism spectrum disorder. *Mol Psychiatry. 2021, 26* (5), 1442-1444. DOI: 10.1038/s41380-020-0778-5
55. Liu Z, Mao X, Dan Z, Pei Y, Xu R, Guo M, Liu K, Zhang F, Chen J, Su C, Zhuang Y, Tang J, Xia Y, Qin L, Hu Z, Liu X. Gene variations in autism spectrum disorder are associated with alteration of gut microbiota, metabolites and cytokines. *Gut Microbes. 2021, 13* (1), 1-16. DOI: 10.1080/19490976.2020.1854967
56. Andeweg SP, Keşmir C, Dutilh BE. Quantifying the impact of human leukocyte antigen on the human gut microbiota. *mSphere. 2021, 6* (4), e0047621. DOI: 10.1128/mSphere.00476-21
57. Theoharides TC, Perlman AI, Twahir A, Kempuraj D. Mast cell activation: beyond histamine and tryptase. *Expert Rev Clin Immunol. 2023, 19* (6), 639-654. DOI: 10.1080/1744666X.2023.2200936
58. Abraham SN, St John AL. Mast cell-orchestrated immunity to pathogens. *Nat Rev Immunol. 2010, 10* (6), 440-52. DOI: 10.1038/nri2782
59. Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders? *Expert Rev Clin Immunol. 2019, 15* (6), 639-656. DOI: 10.1080/1744666X.2019.1596800
60. Kovacheva E, Gevezova M, Maes M, Sarafian V. Mast cells in autism spectrum disorder-the enigma to be solved? *Int J Mol Sci. 2024, 25* (5), 2651. DOI: 10.3390/ijms25052651
61. Boziki M, Theotokis P, Kesidou E, Nella M, Bakirtzis C, Karafoulidou E, Tzitiridou-Chatzopoulou M, Doulberis M, Kazakos E, Deretzi G, Grigoriadis N, Kountouras J. Impact of mast cell activation on neurodegeneration: a potential role for gut-brain axis and h*elicobacter pylori* infection. *Neurol Int. 2024, 16* (6), 1750-1778. DOI: 10.3390/neurolint16060127
62. Amin K. The role of mast cells in allergic inflammation. *Respir Med. 2012, 106* (1), 9-14. DOI: 10.1016/j.rmed.2011.09.007

 doi:10.20944/preprints202506.1715.v1




63. Albert-Bayo M, Paracuellos I, González-Castro AM, Rodríguez-Urrutia A, Rodríguez-Lagunas MJ, Alonso-Cotoner C, Santos J, Vicario M. Intestinal mucosal mast cells: key modulators of barrier function and homeostasis. *Cells. 2019, 8* (2), 135. DOI: 10.3390/cells8020135
64. Theoharides TC, Asadi S, Chen J, Huizinga JD. Irritable bowel syndrome and the elusive mast cells. *Am J Gastroenterol. 2012, 107* (5), 727-9. DOI: 10.1038/ajg.2012.61
65. Petra AI, Panagiotidou S, Hatziagelaki E, Stewart JM, Conti P, Theoharides TC. Gut-microbiota-brain axis and its effect on neuropsychiatric disorders with suspected immune Dysregulation. *Clin Ther. 2015, 37* (5), 984-95. DOI: 10.1016/j.clinthera.2015.04.002
66. Thoo L, Noti M, Krebs P. Keep calm: the intestinal barrier at the interface of peace and war. *Cell Death Dis. 2019, 10* (11), 849. DOI: 10.1038/s41419-019-2086-z
67. Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR, Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. *Intern Emerg Med. 2024, 19* (2), 275-293. DOI: 10.1007/s11739-023-03374-w
68. Potrykus M, Czaja-Stolc S, Stankiewicz M, Kaska Ł, Małgorzewicz S. Intestinal microbiota as a contributor to chronic inflammation and its potential modifications. *Nutrients. 2021, 13* (11), 3839. DOI: 10.3390/nu13113839
69. Solanki R, Karande A, Ranganathan P. Emerging role of gut microbiota dysbiosis in neuroinflammation and neurodegeneration. *Front Neurol. 2023*, 14:1149618. DOI: 10.3389/fneur.2023.1149618
70. Boziki M, Theotokis P, Kesidou E, Nella M, Bakirtzis C, Karafoulidou E, Tzitiridou-Chatzopoulou M, Doulberis M, Kazakos E, Deretzi G, Grigoriadis N, Kountouras J. Impact of mast cell activation on neurodegeneration: a potential role for gut-brain axis and h*elicobacter pylori* infection. *Neurol Int. 2024, 16 (6),* 1750-1778. DOI: 10.3390/neurolint16060127
71. Renga G, Bellet MM, Stincardini C, Pariano M, Oikonomou V, Villella VR, Brancorsini S, Clerici C, Romani L, Costantini C. To be or not to be a pathogen: c*andida albicans* and celiac disease. *Front Immunol. 2019,* 10:2844. DOI: 10.3389/fimmu.2019.02844
72. Smolinska S, Jutel M, Crameri R, O'Mahony L. Histamine and gut mucosal immune regulation. *Allergy. 2014, 69* (3), 273-81. DOI: 10.1111/all.12330
73. Potts RA, Tiffany CM, Pakpour N, Lokken KL, Tiffany CR, Cheung K, Tsolis RM, Luckhart S. Mast cells and histamine alter intestinal permeability during malaria parasite infection. *Immunobiology. 2016, 221* (3) 468-74. DOI: 10.1016/j.imbio.2015.11.003
74. Yue J, Tan Y, Huan R, Guo J, Yang S, Deng M, Xiong Y, Han G, Liu L, Liu J, Cheng Y, Zha Y, Zhang J. Mast cell activation mediates blood-brain barrier impairment and cognitive dysfunction in septic mice in a histamine-dependent pathway. *Front Immunol. 2023,* 14, 1090288. DOI: 10.3389/fimmu.2023.1090288
75. Alizadeh A, Akbari P, Garssen J, Fink-Gremmels J, Braber S. Epithelial integrity, junctional complexes, and biomarkers associated with intestinal functions. *Tissue Barriers. 2022, 10* (3), 1996830. DOI: 10.1080/21688370.2021.1996830
76. Poto R, Fusco W, Rinninella E, Cintoni M, Kaitsas F, Raoul P, Caruso C, Mele MC, Varricchi G, Gasbarrini A, Cammarota G, Ianiro G. The role of gut microbiota and leaky gut in the pathogenesis of food allergy. *Nutrients. 2023, 16* (1), 92. DOI: 10.3390/nu16010092
77. Akbari P, Braber S, Varasteh S, Alizadeh A, Garssen J, Fink-Gremmels J. The intestinal barrier as an emerging target in the toxicological assessment of mycotoxins. *Arch Toxicol. 2017, 91* (3), 1007-1029. DOI: 10.1007/s00204-016-1794-8
78. Akiho H, Ihara E, Nakamura K. Low-grade inflammation plays a pivotal role in gastrointestinal dysfunction in irritable bowel syndrome. *World J Gastrointest Pathophysiol. 2010, 1* (3), 97-105. DOI: 10.4291/wjgp.v1.i3.97
79. Ray K. Bacterial histamine and abdominal pain in IBS. *Nat Rev Gastroenterol Hepatol, 2022, 19* (10), 623. DOI: 10.1038/s41575-022-00681-z
80. Rothenberg ME. An allergic basis for abdominal pain. *N Engl J Med. 2021, 384* (22), 2156-2158. DOI: 10.1056/NEJMcibr2104146
81. Kawamoto S, Maruya M, Kato LM, Suda W, Atarashi K, Doi Y, Tsutsui Y, Qin H, Honda K, Okada T, Hattori M, Fagarasan S. Foxp3(+) T cells regulate immunoglobulin a selection and facilitate diversification

 doi:10.20944/preprints202506.1715.v1



of bacterial species responsible for immune homeostasis. *Immunity. 2014, 41* (1), 152-65. DOI: 10.1016/j.immuni.2014.05.016

82. Zeng MY, Inohara N, Nuñez G. Mechanisms of inflammation-driven bacterial dysbiosis in the gut. *Mucosal Immunol. 2017, 10* (1), 18-26. DOI: 10.1038/mi.2016.75
83. Grenier B, Applegate TJ. Modulation of intestinal functions following mycotoxin ingestion: meta-analysis of published experiments in animals. *Toxins (Basel). 2013, 5* (2), 396-430. DOI: 10.3390/toxins5020396
84. Yang Y, Palm NW. Immunoglobulin A and the microbiome. *Curr Opin Microbiol. 2020, 56,* 89-96. DOI: 10.1016/j.mib.2020.08.003
85. Doron I, Kusakabe T, Iliev ID. Immunoglobulins at the interface of the gut mycobiota and anti-fungal immunity. *Semin Immunol. 2023, 67,* 101757. DOI: 10.1016/j.smim.2023.101757
86. Suzuki K, Ha SA, Tsuji M, Fagarasan S. Intestinal IgA synthesis: a primitive form of adaptive immunity that regulates microbial communities in the gut. *Semin Immunol. 2007, 19* (2), 127-35. DOI: 10.1016/j.smim.2006.10.001
87. Kawamoto S, Maruya M, Kato LM, Suda W, Atarashi K, Doi Y, Tsutsui Y, Qin H, Honda K, Okada T, Hattori M, Fagarasan S. Foxp3(+) T cells regulate immunoglobulin a selection and facilitate diversification of bacterial species responsible for immune homeostasis. *Immunity. 2014, 41* (1), 152-65. DOI: 10.1016/j.immuni.2014.05.016
88. Kato LM, Kawamoto S, Maruya M, Fagarasan S. The role of the adaptive immune system in regulation of gut microbiota. *Immunol Rev. 2014, 260* (1), 67-75. DOI: 10.1111/imr.12185
89. Suhr MJ, Hallen-Adams HE. The human gut mycobiome: pitfalls and potentials--a mycologist's perspective. *Mycologia. 2015, 107* (6), 1057-73. DOI: 10.3852/15-147
90. Renga G, Moretti S, Oikonomou V, Borghi M, Zelante T, Paolicelli G, Costantini C, De Zuani M, Villella VR, Raia V, Del Sordo R, Bartoli A, Baldoni M, Renauld JC, Sidoni A, Garaci E, Maiuri L, Pucillo C, Romani L. IL-9 and mast cells are key players of candida albicans commensalism and pathogenesis in the gut. *Cell Rep. 2018, 23* (6), 1767-1778. DOI: 10.1016/j.celrep.2018.04.034
91. Song P, Peng G, Yue H, Ogawa T, Ikeda S, Okumura K, Ogawa H, Niyonsaba F. Candidalysin, a virulence factor of candida albicans, stimulates mast cells by mediating cross-talk between signaling pathways activated by the dectin-1 receptor and MAPKs. *J Clin Immunol. 2022,* 42 (5), 1009-1025. DOI: 10.1007/s10875-022-01267-9
92. Jiao Q, Luo Y, Scheffel J, Zhao Z, Maurer M. The complex role of mast cells in fungal infections. *Exp Dermatol. 2019, 28* (7), 749-755. DOI: 10.1111/exd.13907
93. De Zuani M, Paolicelli G, Zelante T, Renga G, Romani L, Arzese A, Pucillo CEM, Frossi B. Mast cells respond to *candida albican i*nfections and modulate macrophages phagocytosis of the fungus. *Front Immunol. 2018, 9,* 2829. DOI: 10.3389/fimmu.2018.02829
94. Zhang F, Aschenbrenner D, Yoo JY, Zuo T. The gut mycobiome in health, disease, and clinical applications in association with the gut bacterial microbiome assembly. *Lancet Microbe. 2022, 3* (12), e969-e983. DOI: 10.1016/S2666-5247(22)00203-8
95. Suhr MJ, Hallen-Adams HE. The human gut mycobiome: pitfalls and potentials--a mycologist's perspective. *Mycologia. 2015, 107* (6), 1057-73. DOI: 10.3852/15-147
96. Li XV, Leonardi I, Iliev ID. Gut Mycobiota in Immunity and Inflammatory Disease. *Immunity. 2019, 50* (6), 1365-1379. DOI: 10.1016/j.immuni.2019.05.023
97. Richard ML, Sokol H. The gut mycobiota: insights into analysis, environmental interactions and role in gastrointestinal diseases. *Nat Rev Gastroenterol Hepatol. 2019, 16* (6), 331-345. DOI: 10.1038/s41575-019-0121-2
98. Chua RXY, Tay MJY, Ooi DSQ, Siah KTH, Tham EH, Shek LP, Meaney MJ, Broekman BFP, Loo EXL. Understanding the link between allergy and neurodevelopmental disorders: a current review of factors and mechanisms. *Front Neurol. 2021,* 11:603571. DOI: 10.3389/fneur.2020.603571
99. Su Q, Wong OWH, Lu W, Wan Y, Zhang L, Xu W, Li MKT, Liu C, Cheung CP, Ching JYL, Cheong PK, Leung TF, Chan S, Leung P, Chan FKL, Ng SC. Multikingdom and functional gut microbiota markers for autism spectrum disorder. *Nat Microbiol. 2024, 9* (9), 2344-2355. DOI: 10.1038/s41564-024-01739-1. Epub 2024 Jul 8. Erratum in: Nat Microbiol. 2025 Feb;10(2):600. doi: 10.1038/s41564-024-01900-w

 doi:10.20944/preprints202506.1715.v1




100. Li Q, Han Y, Dy ABC, Hagerman RJ. The gut microbiota and autism spectrum disorders. *Front Cell Neurosci. 2017, 11,* 120. DOI: 10.3389/fncel.2017.00120
101. Li D, Wu M. Pattern recognition receptors in health and diseases. *Signal Transduct Target Ther. 2021, 6* (1), 291. DOI: 10.1038/s41392-021-00687-0
102. Liew WP, Mohd-Redzwan S. mycotoxin: its impact on gut health and microbiota. *Front Cell Infect Microbiol. 2018,* 8:60. DOI: 10.3389/fcimb.2018.00060
103. Kim JY, Choi MJ, Ha S, Hwang J, Koyanagi A, Dragioti E, Radua J, Smith L, Jacob L, Salazar de Pablo G, Lee SW, Yon DK, Thompson T, Cortese S, Lollo G, Liang CS, Chu CS, Fusar-Poli P, Cheon KA, Shin JI, Solmi M. Association between autism spectrum disorder and inflammatory bowel disease: A systematic review and meta-analysis. *Autism Res. 2022, 15* (2), 340-352. DOI: 10.1002/aur.2656
104. Zhao Y, Jaber VR, Pogue AI, Sharfman NM, Taylor C, Lukiw WJ. Lipopolysaccharides (LPSs) as potent neurotoxic glycolipids in alzheimer's disease (AD). *Int J Mol Sci. 2022, 23 (20),* 12671. DOI: 10.3390/ijms232012671
105. Candelli M, Franza L, Pignataro G, Ojetti V, Covino M, Piccioni A, Gasbarrini A, Franceschi F. Interaction between Lipopolysaccharide and Gut Microbiota in Inflammatory Bowel Diseases. *Int J Mol Sci. 2021, 22* (12), 6242. DOI: 10.3390/ijms22126242
106. Violi F, Cammisotto V, Bartimoccia S, Pignatelli P, Carnevale R, Nocella C. Gut-derived low-grade endotoxaemia, atherothrombosis and cardiovascular disease. *Nat Rev Cardiol. 2023, 20* (1), 24-37. DOI: 10.1038/s41569-022-00737-2
107. Emanuele E, Orsi P, Boso M, Broglia D, Brondino N, Barale F, di Nemi SU, Politi P. Low-grade endotoxemia in patients with severe autism. *Neurosci Lett. 2010, 471* (3), 162-5. DOI: 10.1016/j.neulet.2010.01.033
108. Li F, Ke H, Wang S, Mao W, Fu C, Chen X, Fu Q, Qin X, Huang Y, Li B, Li S, Xing J, Wang M, Deng W. Leaky gut plays a critical role in the pathophysiology of autism in mice by activating the Llpopolysaccharide-mediated toll-like receptor 4-myeloid differentiation factor 88-nuclear factor kappa b signaling pathway. *Neurosci Bull. 2023, 39* (6), 911-928. DOI: 10.1007/s12264-022-00993-9
109. Xiao L, Yan J, Feng D, Ye S, Yang T, Wei H, Li T, Sun W, Chen J. Critical Role of TLR4 on the microglia activation induced by maternal LPS exposure leading to ASD-like behavior of offspring. *Front Cell Dev Biol. 2021, 9,* 634837.DOI: 10.3389/fcell.2021.634837
110. Kirsten TB, Chaves-Kirsten GP, Chaible LM, Silva AC, Martins DO, Britto LR, Dagli ML, Torrão AS, Palermo-Neto J, Bernardi MM. Hypoactivity of the central dopaminergic system and autistic-like behavior induced by a single early prenatal exposure to lipopolysaccharide. *J Neurosci Res. 2012, 90* (10), 1903-12. DOI: 10.1002/jnr.23089
111. Kirsten TB, Taricano M, Maiorka PC, Palermo-Neto J, Bernardi MM. Prenatal lipopolysaccharide reduces social behavior in male offspring. *Neuroimmunomodulation. 2010, 17* (4), 240-51. DOI: 10.1159/000290040
112. Kirsten TB, Palermo-Neto J, Bernardi MM. A rat model of autism induced by a single early prenatal exposure to LPS. *Brain, Behavior, and Immunity. 2012, 26* (1), S4. DOI: 10.1016/j.bbi.2012.07.035
113. Tadas M, Wankhede N, Chandurkar P, Kotagale N, Umekar M, Katariya R, Waghade A, Kokare D, Taksande B. Postnatal propionic acid exposure disrupts hippocampal agmatine homeostasis leading to social deficits and cognitive impairment in autism spectrum disorder-like phenotype in rats. *Pharmacol Biochem Behav. 2025,* 174030. DOI: 10.1016/j.pbb.2025.174030
114. Benitah KC, Kavaliers M, Ossenkopp KP. The enteric metabolite, propionic acid, impairs social behavior and increases anxiety in a rodent ASD model: Examining sex differences and the influence of the estrous cycle. *Pharmacol Biochem Behav. 2023, 231,* 173630. DOI: 10.1016/j.pbb.2023.173630
115. Brown GC. The endotoxin hypothesis of neurodegeneration. *J Neuroinflammation. 2019, 6* (1), 180. DOI: 10.1186/s12974-019-1564-7
116. Saresella M, Piancone F, Marventano I, Zoppis M, Hernis A, Zanette M, Trabattoni D, Chiappedi M, Ghezzo A, Canevini MP, la Rosa F, Esposito S, Clerici M. Multiple inflammasome complexes are activated in autistic spectrum disorders. *Brain Behav Immun. 2016, 57,* 125-133. DOI: 10.1016/j.bbi.2016.03.009
117. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An overview of mechanisms of activation and regulation. *Int J Mol Sci. 2019, 20* (13), 3328. DOI: 10.3390/ijms20133328

 doi:10.20944/preprints202506.1715.v1




118. Rogiers O, Frising UC, Kucharíková S, Jabra-Rizk MA, van Loo G, Van Dijck P, Wullaert A. Candidalysin crucially contributes to nlrp3 inflammasome activation by candida albicans hyphae. *mBio. 2019, 10* (1), e02221-18. DOI: 10.1128/mBio.02221-18
119. McCurdy JD, Lin TJ, Marshall JS. Toll-like receptor 4-mediated activation of murine mast cells. *J Leukoc Biol. 2001, 70* (6), 977-84
120. Yu M, Song XT, Liu B, Luan TT, Liao SL, Zhao ZT. The emerging role of mast cells in response to fungal infection. *Front Immunol. 2021, 12*, 688659. DOI: 10.3389/fimmu.2021.688659
121. Gonzalez A, Hammock EAD. Oxytocin and microglia in the development of social behaviour. *Philos Trans R Soc Lond B Biol Sci. 2022, 377* (1858), 20210059. DOI: 10.1098/rstb.2021.0059
122. Caetano-Silva ME, Rund L, Vailati-Riboni M, Matt S, Soto-Diaz K, Beever J, Allen JM, Woods JA, Steelman AJ, Johnson RW. The emergence of inflammatory microglia during gut inflammation is not affected by FFAR2 expression in intestinal epithelial cells or peripheral myeloid cells. *Brain Behav Immun. 2024, 118*, 423-436. DOI: 10.1016/j.bbi.2024.03.016
123. Abdel-Haq R, Schlachetzki JCM, Glass CK, Mazmanian SK. Microbiome-microglia connections via the gut-brain axis. *J Exp Med. 2019, 216* (1), 41-59. DOI: 10.1084/jem.20180794
124. Qin L, Li G, Qian X, Liu Y, Wu X, Liu B, Hong JS, Block ML. Interactive role of the toll-like receptor 4 and reactive oxygen species in LPS-induced microglia activation. *Glia. 2005, 52* (1), 78-84. DOI: 10.1002/glia.20225
125. Chen Z, Jalabi W, Shpargel KB, Farabaugh KT, Dutta R, Yin X, Kidd GJ, Bergmann CC, Stohlman SA, Trapp BD. Lipopolysaccharide-induced microglial activation and neuroprotection against experimental brain injury is independent of hematogenous TLR4. *J Neurosci. 2012, 32* (34), 11706-15. DOI: 10.1523/JNEUROSCI.0730-12.2012
126. Ye X, Zhu M, Che X, Wang H, Liang XJ, Wu C, Xue X, Yang J. Lipopolysaccharide induces neuroinflammation in microglia by activating the MTOR pathway and downregulating Vps34 to inhibit autophagosome formation. *J Neuroinflammation*. 2020, 17 (1), 18. DOI: 10.1186/s12974-019-1644-8
127. Jung H, Lee D, You H, Lee M, Kim H, Cheong E, Um JW. LPS induces microglial activation and GABAergic synaptic deficits in the hippocampus accompanied by prolonged cognitive impairment. *Sci Rep. 2023, 13* (1), 6547. DOI: 10.1038/s41598-023-32798-9
128. Gozal E, Jagadapillai R, Cai J, Barnes GN. Potential crosstalk between sonic hedgehog-WNT signaling and neurovascular molecules: Implications for blood-brain barrier integrity in autism spectrum disorder. *J Neurochem. 2021, 159* (1) 15-28. DOI: 10.1111/jnc.15460
129. Wei H, Alberts I, Li X. The apoptotic perspective of autism. *Int J Dev Neurosci. 2014, 36*, 13-8. DOI: 10.1016/j.ijdevneu.2014.04.004
130. Hines DJ, Choi HB, Hines RM, Phillips AG, MacVicar BA. Prevention of LPS-induced microglia activation, cytokine production and sickness behavior with TLR4 receptor interfering peptides. *PLoS One. 2013, 8* (3), e60388. DOI: 10.1371/journal.pone.0060388
131. Bassi GS, Kanashiro A, Santin FM, de Souza GE, Nobre MJ, Coimbra NC. Lipopolysaccharide-induced sickness behaviour evaluated in different models of anxiety and innate fear in rats. *Basic Clin Pharmacol Toxicol. 2012, 110* (4), 359-69. DOI: 10.1111/j.1742-7843.2011.00824.x
132. Biesmans S, Meert TF, Bouwknecht JA, Acton PD, Davoodi N, De Haes P, Kuijlaars J, Langlois X, Matthews LJ, Ver Donck L, Hellings N, Nuydens R. Systemic immune activation leads to neuroinflammation and sickness behavior in mice. *Mediators Inflamm. 2013*, 271359. DOI: 10.1155/2013/271359
133. Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. *Brain Behav Immun. 2012, 26* (3), 383-92. DOI: 10.1016/j.bbi.2011.08.007
134. Behrens M, Hüwel S, Galla HJ, Humpf HU. Blood-Brain Barrier Effects of the Fusarium Mycotoxins Deoxynivalenol, 3 Acetyldeoxynivalenol, and moniliformin and their transfer to the brain. *PLoS One. 2015, 10* (11), e0143640. DOI: 10.1371/journal.pone.0143640
135. Patel R, Hossain MA, German N, Al-Ahmad AJ. Gliotoxin penetrates and impairs the integrity of the human blood-brain barrier in vitro. *Mycotoxin Res. 2018, 34* (4), 257-268. DOI: 10.1007/s12550-018-0320-7
136. Doi K, Uetsuka K. Mechanisms of mycotoxin-induced neurotoxicity through oxidative stress-associated pathways. *Int J Mol Sci. 2011, 12* (8), 5213-37. DOI: 10.3390/ijms12085213

 doi:10.20944/preprints202506.1715.v1




137. Abbott NJ. Inflammatory mediators and modulation of blood-brain barrier permeability. *Cell Mol Neurobiol. 2000, 20* (2), 131-47. DOI: 10.1023/a:1007074420772
138. Song Z, Song R, Liu Y, Wu Z, Zhang X. Effects of ultra-processed foods on the microbiota-gut-brain axis: The bread-and-butter issue. *Food Res Int. 2023, 167,* 112730. DOI: 10.1016/j.foodres.2023.112730
139. Theoharides TC, Konstantinidou AD. Corticotropin-releasing hormone and the blood-brain-barrier. *Front Biosci. 2007, 12,* 1615-28.DOI: 10.2741/2174
140. Esposito P, Chandler N, Kandere K, Basu S, Jacobson S, Connolly R, Tutor D, Theoharides TC. Corticotropin-releasing hormone and brain mast cells regulate blood-brain-barrier permeability induced by acute stress. *J Pharmacol Exp Ther. 2002, 303* (3), 1061-6. DOI: 10.1124/jpet.102.038497
141. Theoharides TC. Mast cells: the immune gate to the brain. *Life Sci. 1990,46* (9), 607-17. DOI: 10.1016/0024-3205(90)90129-f
142. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, Ransohoff RM, Greenberg ME, Barres BA, Stevens B. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron. 2012, 74* (4), 691-705. DOI: 10.1016/j.neuron.2012.03.026
143. Gonzalez A, Hammock EAD. Oxytocin and microglia in the development of social behaviour. *Philos Trans R Soc Lond B Biol Sci. 2022, 377* (1858), 20210059. DOI: 10.1098/rstb.2021.0059
144. Xiong Y, Chen J, Li Y. Microglia and astrocytes underlie neuroinflammation and synaptic susceptibility in autism spectrum disorder. *Front Neurosci. 2023, 17,* 1125428. DOI: 10.3389/fnins.2023.1125428
145. McNamara NB, Munro DAD, Bestard-Cuche N, Uyeda A, Bogie JFJ, Hoffmann A, Holloway RK, Molina-Gonzalez I, Askew KE, Mitchell S, Mungall W, Dodds M, Dittmayer C, Moss J, Rose J, Szymkowiak S, Amann L, McColl BW, Prinz M, Spires-Jones TL, Stenzel W, Horsburgh K, Hendriks JJA, Pridans C, Muramatsu R, Williams A, Priller J, Miron VE. Microglia regulate central nervous system myelin growth and integrity. *Nature. 2023, 613* (7942), 120-129. DOI: 10.1038/s41586-022-05534-y
146. Xu T, Liu C, Deng S, Gan L, Zhang Z, Yang GY, Tian H, Tang Y. The roles of microglia and astrocytes in myelin phagocytosis in the central nervous system. *J Cereb Blood Flow Metab. 2023, 43* (3), 325-340. DOI: 10.1177/0271678X221137762
147. Marín-Teva JL, Cuadros MA, Martín-Oliva D, Navascués J. Microglia and neuronal cell death. *Neuron Glia Biol. 2011, 7* (1), 25-40. DOI: 10.1017/S1740925X12000014
148. Tay TL, Béchade C, D'Andrea I, St-Pierre MK, Henry MS, Roumier A, Tremblay ME. Microglia gone rogue: impacts on lsychiatric disorders across the lifespan. *Front Mol Neurosci. 2018, 10,* 421. DOI: 10.3389/fnmol.2017.00421
149. Rodriguez JI, Kern JK. Evidence of microglial activation in autism and its possible role in brain underconnectivity. *Neuron Glia Biol. 2011, 7* (2-4), 205-13. DOI: 10.1017/S1740925X12000142
150. Gupta S, Ellis SE, Ashar FN, Moes A, Bader JS, Zhan J, West AB, Arking DE. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. *Nat Commun. 2014, 5,* 5748. DOI: 10.1038/ncomms6748
151. Frick LR, Williams K, Pittenger C. Microglial dysregulation in psychiatric disease. *Clin Dev Immunol. 2013,* 608654. DOI: 10.1155/2013/608654
152. Petrelli F, Pucci L, Bezzi P. Astrocytes and microglia and their potential link with autism spectrum disorders. *Front Cell Neurosci. 2016,* 10, 21. DOI: 10.3389/fncel.2016.00021
153. Theoharides TC, Kavalioti M, Tsilioni I. Mast cells, stress, fear and autism spectrum disorder. *Int J Mol Sci. 2019, 20* (15), 3611. DOI: 10.3390/ijms20153611
154. Gouveia FV, Hamani C, Fonoff ET, Brentani H, Alho EJL, de Morais RMCB, de Souza AL, Rigonatti SP, Martinez RCR. Amygdala and hypothalamus: historical overview with focus on aggression. *Neurosurgery. 2019, 85* (1), 11-30. DOI: 10.1093/neuros/nyy635
155. Melbourne JK, Chandler CM, Van Doorn CE, Bardo MT, Pauly JR, Peng H, Nixon K. Primed for addiction: A critical review of the role of microglia in the neurodevelopmental consequences of adolescent alcohol drinking. *Alcohol Clin Exp Res. 2021, 45* (10), 1908-1926. DOI: 10.1111/acer.14694
156. da Silva MCM, Iglesias LP, Candelario-Jalil E, Khoshbouei H, Moreira FA, de Oliveira ACP. Role of microglia in psychostimulant addiction. *Curr Neuropharmacol. 2023, 21* (2), 235-259. DOI: 10.2174/1570159X21666221208142151

 doi:10.20944/preprints202506.1715.v1




157. Won E, Kim YK. Neuroinflammation-associated alterations of the brain as potential neural biomarkers in anxiety disorders. *Int J Mol Sci. 2020 , 21* (18), 6546. DOI: 10.3390/ijms21186546
158. Luo Y. The crosstalk between the "inflamed" mind and the "impulsive" mind: activation of microglia and impulse control disorders. *Second International Conference on Biological Engineering and Medical Science. 2023*, 126112H. DOI: 10.1117/12.2669957
159. Yokokura M, Takebasashi K, Takao A, Nakaizumi K, Yoshikawa E, Futatsubashi M, Suzuki K, Nakamura K, Yamasue H, Ouchi Y. In vivo imaging of dopamine D1 receptor and activated microglia in attention-deficit/hyperactivity disorder: a positron emission tomography study. *Mol Psychiatry. 2021, 26* (9), 4958-4967. DOI: 10.1038/s41380-020-0784-7
160. Zhu H, Guan A, Liu J, Peng L, Zhang Z, Wang S. Noteworthy perspectives on microglia in neuropsychiatric disorders. *J Neuroinflammation. 2023, 20* (1), 223. DOI: 10.1186/s12974-023-02901-y
161. Underwood JFG, DelPozo-Banos M, Frizzati A, Rai D, John A, Hall J. Neurological and psychiatric disorders among autistic adults: a population healthcare record study. *Psychol Med. 2023, 53* (12), 5663-5673. DOI: 10.1017/S0033291722002884
162. White SW, Oswald D, Ollendick T, Scahill L. Anxiety in children and adolescents with autism spectrum disorders. *Clin Psychol Rev. 2009, 29* (3), 216-29. DOI: 10.1016/j.cpr.2009.01.003
163. Montaser J, Umeano L, Pujari HP, Nasiri SMZ, Parisapogu A, Shah A, Khan S. Correlations between the development of social anxiety and individuals with autism spectrum disorder: a systematic review. *Cureus. 2023, 15* (9), e44841. DOI: 10.7759/cureus.44841
164. Mayes SD, Calhoun SL, Aggarwal R, Baker C, Mathapati S, Molitoris S, Mayes RD. Unusual fears in children with autism. *Research in Autism Spectrum Disorders. 2013, 7* (1), 151-158. DOI: 10.1016/j.rasd.2012.08.002
165. Patel S, Day TN, Jones N, Mazefsky CA. Association between anger rumination and autism symptom severity, depression symptoms, aggression, and general dysregulation in adolescents with autism spectrum disorder. *Autism. 2017, 21* (2), 181-189. DOI: 10.1177/1362361316633566
166. Lugo-Huitrón R, Ugalde Muñiz P, Pineda B, Pedraza-Chaverrí J, Ríos C, Pérez-de la Cruz V. Quinolinic acid: an endogenous neurotoxin with multiple targets. *Oxid Med Cell Longev. 2013,* 104024. DOI: 10.1155/2013/104024
167. Yildirim V, Simsek S, Cetin I, Dokuyucu R. Kynurenine, kynurenic acid, quinolinic acid and interleukin-6 levels in the serum of patients with autism spectrum disorder. *Medicina (Kaunas). 2023, 59* (11), 1906. DOI: 10.3390/medicina59111906
168. Carthy E, Ellender T. Histamine, Neuroinflammation and Neurodevelopment: A Review. *Front Neurosci. 2021, 15,* 680214. DOI: 10.3389/fnins.2021.680214
169. Lasselin J, Lekander M, Benson S, Schedlowski M, Engler H. Sick for science: experimental endotoxemia as a translational tool to develop and test new therapies for inflammation-associated depression. *Mol Psychiatry. 2021, 26* (8), 3672-3683. DOI: 10.1038/s41380-020-00869-2
170. Theoharides TC. Mast cells: the immune gate to the brain. *Life Sci. 1990, 46* (9), 607-17. DOI: 10.1016/0024-3205(90)90129-f
171. Skaper SD, Facci L, Giusti P. Mast cells, glia and neuroinflammation: partners in crime? *Immunology. 2014, 141*, (3), 314-27. DOI: 10.1111/imm.12170
172. Zhang S, Zeng X, Yang H, Hu G, He S. Mast cell tryptase induces microglia activation via protease-activated receptor 2 signaling. *Cell Physiol Biochem. 2012, 29* (5-6), 931-40. DOI: 10.1159/000171029
173. Zhang X, Wang Y, Dong H, Xu Y, Zhang S. Induction of microglial activation by mediators released from mast cells. *Cell Physiol Biochem. 2016, 38*, (4), 1520-31. DOI: 10.1159/000443093
174. Conesa MPB, Blixt FW, Peesh P, Khan R, Korf J, Lee J, Jagadeesan G, Andersohn A, Das TK, Tan C, Di Gesu C, Colpo GD, Moruno-Manchón JF, McCullough LD, Bryan R, Ganesh BP. Stabilizing histamine release in gut mast cells mitigates peripheral and central inflammation after stroke. *J Neuroinflammation. 2023, 20,* (1), 230. DOI: 10.1186/s12974-023-02887-7
175. Theoharides TC, Kavalioti M, Tsilioni I. Mast cells, stress, fear and autism spectrum disorder. *Int J Mol Sci. 2019, 20,* (15), 3611. DOI: 10.3390/ijms20153611

 doi:10.20944/preprints202506.1715.v1




176. Theoharides TC. The impact of psychological stress on mast cells. *Ann Allergy Asthma Immunol. 2020, 25,* (4), 388-392. DOI: 10.1016/j.anai.2020.07.007
177. Theoharides TC, Stewart JM, Panagiotidou S, Melamed I. Mast cells, brain inflammation and autism. *Eur J Pharmacol. 2016, 778*, 96-102. DOI: 10.1016/j.ejphar.2015.03.086
178. Theoharides TC, Doyle R. Autism, gut-blood-brain barrier, and mast cells. *J Clin Psychopharmacol. 2008, 28,* (5), 479-83. DOI: 10.1097/JCP.0b013e3181845f48
179. Theoharides TC, Zhang B. Neuro-inflammation, blood-brain barrier, seizures and autism. *J Neuroinflammation. 2011, 8,* 168. DOI: 10.1186/1742-2094-8-168
180. Theoharides TC. Is a subtype of autism an allergy of the brain? *Clin Ther. 2013, 35,* (5), 584-91. DOI: 10.1016/j.clinthera.2013.04.009
181. Theoharides TC, Stewart JM, Panagiotidou S, Melamed I. Mast cells, brain inflammation and autism. *Eur J Pharmacol. 2016, 778,* 96-102. DOI: 10.1016/j.ejphar.2015.03.086
182. Theoharides TC, Asadi S, Panagiotidou S, Weng Z. The "missing link" in autoimmunity and autism: extracellular mitochondrial components secreted from activated live mast cells. *Autoimmun Rev. 2013, 12,* (12), 1136-42. DOI: 10.1016/j.autrev.2013.06.018
183. Lauritzen KH, Moldestad O, Eide L, Carlsen H, Nesse G, Storm JF, Mansuy IM, Bergersen LH, Klungland A. Mitochondrial DNA toxicity in forebrain neurons causes apoptosis, neurodegeneration, and impaired behavior. *Mol Cell Biol. 2010, 30,* (6), 1357-67. DOI: 10.1128/MCB.01149-09
184. Duncan JG, Waton NG. Absorption of histamine from the gastrointestinal tract of dogs in vivo. *J Physiol. 1968 , 198,* (3), 505-15. DOI: 10.1113/jphysiol.1968.sp008621
185. Scammell TE, Jackson AC, Franks NP, Wisden W, Dauvilliers Y. Histamine: neural circuits and new medications. *Sleep. 2019, 42,* (1), zsy183. DOI: 10.1093/sleep/zsy183
186. Wang Y, Sha H, Zhou L, Chen Y, Zhou Q, Dong H, Qian Y. The Mast Cell Is an Early Activator of Lipopolysaccharide-Induced Neuroinflammation and blood-brain barrier dysfunction in the jippocampus. *Mediators Inflamm. 2020,* 8098439. DOI: 10.1155/2020/8098439
187. Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. *Physiol Rev. 2008, 88,* (3), 1183-241. DOI: 10.1152/physrev.00043.2007
188. Devnani PA, Hegde AU. Autism and sleep disorders. *J Pediatr Neurosci. 2015, 10* (4), 304-7. DOI: 10.4103/1817-1745.174438
189. Ji W, Suga N. Histaminergic modulation of nonspecific plasticity of the auditory system and differential gating. *J Neurophysiol. 2013, 109,* (3), 792-802. DOI: 10.1152/jn.00930.2011
190. Fabian R, Seyfarth EA. Acetylcholine and histamine are transmitter candidates in identifiable mechanosensitive neurons of the spider Cupiennius salei: an immunocytochemical study. *Cell Tissue Res. 1997, 287,* (2), 413-23. DOI: 10.1007/s004410050766
191. Orona E, Ache BW. Physiological and pharmacological evidence for histamine as a neurotransmitter in the olfactory CNS of the spiny lobster. *Brain Res. 1992, 590,* (1-2), 136-43. DOI: 10.1016/0006-8993(92)91089-w
192. Saure E, Lepistö-Paisley T, Raevuori A, Laasonen M. Atypical sensory processing is associated with lower body mass index and increased aating disturbance in individuals with anorexia nervosa. *Front Psychiatry. 2022, 13*, 850594. DOI: 10.3389/fpsyt.2022.850594
193. Kojovic N, Ben Hadid L, Franchini M, Schaer M. Sensory processing issues and their association with social difficulties in children with autism spectrum disorders. *J Clin Med. 2019, 8* (10), 1508. DOI: 10.3390/jcm8101508
194. Kim JY, Choi MJ, Ha S, Hwang J, Koyanagi A, Dragioti E, Radua J, Smith L, Jacob L, Salazar de Pablo G, Lee SW, Yon DK, Thompson T, Cortese S, Lollo G, Liang CS, Chu CS, Fusar-Poli P, Cheon KA, Shin JI, Solmi M. Association between autism spectrum disorder and inflammatory bowel disease: A systematic review and meta-analysis. *Autism Res. 2022, 15* (2), 340-352. DOI: 10.1002/aur.2656
195. Fu J, Zheng Y, Gao Y, Xu W. Dietary Fiber Intake and Gut Microbiota in Human Health. *Microorganisms. 2022, 10* (12), 2507. DOI: 10.3390/microorganisms10122507
196. Hoffmann C, Dollive S, Grunberg S, Chen J, Li H, Wu GD, Lewis JD, Bushman FD. Archaea and fungi of the human gut microbiome: correlations with diet and bacterial residents. *PLoS One. 2013, 8* (6), e66019. DOI: 10.1371/journal.pone.0066019

 doi:10.20944/preprints202506.1715.v1




197. Erlanson-Albertsson C, Stenkula KG. The importance of food for endotoxemia and an inflammatory response. *Int J Mol Sci. 2021, 22* (17), 9562. DOI: 10.3390/ijms22179562
198. Jochum C. Histamine intolerance: symptoms, diagnosis, and beyond. *Nutrients. 2024, 16* (8), 1219. DOI: 10.3390/nu16081219
199. Tsilioni I, Taliou A, Francis K, Theoharides TC. Children with autism spectrum disorders, who improved with a luteolin-containing dietary formulation, show reduced serum levels of TNF and IL-6. *Transl Psychiatry. 2015, 5* (9), e647. DOI: 10.1038/tp.2015.142
200. Theoharides TC, Asadi S, Panagiotidou S. A case series of a luteolin formulation (NeuroProtek®) in children with autism spectrum disorders. *Int J Immunopathol Pharmacol. 2012, 25* (2), 317-23. DOI: 10.1177/039463201202500201
201. Taliou A, Zintzaras E, Lykouras L, Francis K. An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behavior in children with autism spectrum disorders. *Clin Ther. 2013, 35* (5), 592-602. DOI: 10.1016/j.clinthera.2013.04.006
202. Lin Y, Shi R, Wang X, Shen HM. Luteolin, a flavonoid with potential for cancer prevention and therapy. *Curr Cancer Drug Targets. 2008, 8* (7), 634-46. DOI: 10.2174/156800908786241050
203. Theoharides TC. Luteolin: The wonder flavonoid. *Biofactors. 2021, 47* (2), 139-140. DOI: 10.1002/biof.1729
204. Huang L, Kim MY, Cho JY. Immunopharmacological activities of luteolin in chronic diseases. *Int J Mol Sci. 2023, 24* (3), 2136. DOI: 10.3390/ijms24032136
205. Theoharides TC, Kempuraj D, Iliopoulou BP. Mast cells, T cells, and inhibition by luteolin: implications for the pathogenesis and treatment of multiple sclerosis. *Adv Exp Med Biol. 2007, 601*, 423-30. DOI: 10.1007/978-0-387-72005-0_45
206. Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders? *Expert Rev Clin Immunol. 2019, 15* (6), 639-656. DOI: 10.1080/1744666X.2019.1596800
207. Tsilioni I, Taliou A, Francis K, Theoharides TC. Children with autism spectrum disorders, who improved with a luteolin-containing dietary formulation, show reduced serum levels of TNF and IL-6. *Transl Psychiatry. 2015, 5* (9), e647. DOI: 10.1038/tp.2015.142
208. Tsilioni I, Theoharides T. Luteolin is more potent than cromolyn in their ability to inhibit mediator release from cultured human mast cells. *Int Arch Allergy Immunol. 2024, 185* (8), 803-809. DOI: 10.1159/000537752
209. Jang S, Dilger RN, Johnson RW. Luteolin inhibits microglia and alters hippocampal-dependent spatial working memory in aged mice. *J Nutr. 2010, 140* (10), 1892-8. DOI: 10.3945/jn.110.123273
210. Burton MD, Rytych JL, Amin R, Johnson RW. Dietary luteolin reduces proinflammatory microglia in the brain of senescent mice. *Rejuvenation Res. 2016, 19* (4), 286-92. DOI: 10.1089/rej.2015.1708
211. Chagas MDSDS, Moragas Tellis CJ, Silva AR, Brito MADSM, Teodoro AJ, de Barros Elias M, Ferrarini SR, Behrens MD, Gonçalves-de-Albuquerque CF. Luteolin: A novel approach to fight bacterial infection. *Microb Pathog. 2025, 204*, 107519. DOI: 10.1016/j.micpath.2025.107519
212. Weng Z, Zhang B, Asadi S, Sismanopoulos N, Butcher A, Fu X, Katsarou-Katsari A, Antoniou C, Theoharides TC. Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans. *PLoS One. 2012, 7* (3), e33805. DOI: 10.1371/journal.pone.0033805
213. Jafarinia M, Sadat Hosseini M, Kasiri N, Fazel N, Fathi F, Ganjalikhani Hakemi M, Eskandari N. Quercetin with the potential effect on allergic diseases. *Allergy Asthma Clin Immunol. 2020, 16*,36. DOI: 10.1186/s13223-020-00434-0
214. Shi T, Bian X, Yao Z, Wang Y, Gao W, Guo C. Quercetin improves gut dysbiosis in antibiotic-treated mice. *Food Funct. 2020, 11* (9), 8003-8013. DOI: 10.1039/d0fo01439g
215. Feng J, Li Z, Ma H, Yue Y, Hao K, Li J, Xiang Y, Min Y. Quercetin alleviates intestinal inflammation and improves intestinal functions via modulating gut microbiota composition in LPS-challenged laying hens. *Poult Sci. 2023, 102* (3), 102433. DOI: 10.1016/j.psj.2022.102433
216. Papadopoulou P, Polissidis A, Kythreoti G, Sagnou M, Stefanatou A, Theoharides TC. Anti-inflammatory and neuroprotective polyphenols derived from the european olive tree, *Olea europaea* L., in long COVID

 doi:10.20944/preprints202506.1715.v1



and other conditions involving cognitive impairment. *Int J Mol Sci. 2024, 25* (20), 11040. DOI: 10.3390/ijms252011040.

217. Theoharides TC. Luteolin supplements: All that glitters is not gold. *Biofactors. 2021, 47* (2), 242-244. DOI: 10.1002/biof.1689
218. Duda-Chodak A. The inhibitory effect of polyphenols on human gut microbiota. *J Physiol Pharmacol. 2012, 63* (5), 497-503
219. Patel AB, Tsilioni I, Leeman SE, Theoharides TC. Neurotensin stimulates sortilin and mTOR in human microglia inhibitable by methoxyluteolin, a potential therapeutic target for autism. Proc Natl Acad Sci U S A. 2016 Nov 8;113(45):E7049-E7058. doi: 10.1073/pnas.1604992113. Epub 2016 Sep 23. Erratum in: Proc Natl Acad Sci U S A. 2016 Nov 8;113(45):E7138. doi: 10.1073/pnas.1616587113. PMID: 27663735; PMCID: PMC5111711.
220. Patel AB, Theoharides TC. Methoxyluteolin inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. *J Pharmacol Exp Ther. 2017, 361* (3), 462-471. DOI: 10.1124/jpet.117.240564
221. Taracanova A, Tsilioni I, Conti P, Norwitz ER, Leeman SE, Theoharides TC. Substance P and IL-33 administered together stimulate a marked secretion of IL-1β from human mast cells, inhibited by methoxyluteolin. *Proc Natl Acad Sci U S A. 2018, 115* (40), E9381-E9390. DOI: 10.1073/pnas.1810133115
222. Bawazeer MA, Theoharides TC. IL-33 stimulates human mast cell release of CCL5 and CCL2 via MAPK and NF-κB, inhibited by methoxyluteolin. *Eur J Pharmacol. 2019, 865,* 172760.DOI: 10.1016/j.ejphar.2019.172760
223. Weng Z, Patel AB, Panagiotidou S, Theoharides TC. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. *J Allergy Clin Immunol. 2015, 135* (4), 1044-1052.e5. DOI: 10.1016/j.jaci.2014.10.032
224. Theoharides TC, Stewart JM, Tsilioni I. Tolerability and benefit of a tetramethoxyluteolin-containing skin lotion. *Int J Immunopathol Pharmacol. 2017, 30* (2), 146-151. DOI: 10.1177/0394632017707610
225. De Filippis D, Negro L, Vaia M, Cinelli MP, Iuvone T. New insights in mast cell modulation by palmitoylethanolamide. *CNS Neurol Disord Drug Targets. 2013, 12* (1), 78-83. DOI: 10.2174/18715273113120100013
226. Petrosino S, Schiano Moriello A. Palmitoylethanolamide: a nutritional approach to keep neuroinflammation within physiological boundaries-a systematic review. *Int J Mol Sci. 2020, 21* (24), 9526. DOI: 10.3390/ijms21249526
227. Landolfo E, Cutuli D, Petrosini L, Caltagirone C. Effects of palmitoylethanolamide on neurodegenerative diseases: a review from rodents to humans. *Biomolecules. 2022, 12* (5), 667. DOI: 10.3390/biom12050667.
228. Cerrato S, Brazis P, della Valle MF, Miolo A, Puigdemont A. Effects of palmitoylethanolamide on immunologically induced histamine, PGD2 and TNFalpha release from canine skin mast cells. *Vet Immunol Immunopathol. 2010 Jan 15,* 133 (1), 9-15. DOI: 10.1016/j.vetimm.2009.06.011
229. D'Aloia A, Molteni L, Gullo F, Bresciani E, Artusa V, Rizzi L, Ceriani M, Meanti R, Lecchi M, Coco S, Costa B, Torsello A. Palmitoylethanolamide modulation of microglia activation: characterization of mechanisms of action and implication for Its neuroprotective effects. *Int J Mol Sci. 2021, 22* (6), 3054. DOI: 10.3390/ijms22063054
230. Antonucci N, Cirillo A, Siniscalco D. Beneficial effects of palmitoylethanolamide on expressive language, cognition, and behaviors in autism: a report of two cases. *Case Rep Psychiatry. 2015,* 325061. DOI: 10.1155/2015/325061
231. Nosková E, Vochosková K, Knop V, Stopková P, Kopeček M. Histamine intolerance and anxiety disorders: pilot cross-sectional study of histamine intolerance prevalence in cohort of patients with anxiety disorders. *Eur Psychiatry. 2022, 65* (Suppl 1), S387–8. DOI: 10.1192/j.eurpsy.2022.980
232. Schnedl WJ, Schenk M, Lackner S, Enko D, Mangge H, Forster F. Diamine oxidase supplementation improves symptoms in patients with histamine intolerance. *Food Sci Biotechnol. 2019, 28* (6), 1779-1784. DOI: 10.1007/s10068-019-00627-3
233. Izquierdo-Casas J, Comas-Basté O, Latorre-Moratalla ML, Lorente-Gascón M, Duelo A, Soler-Singla L, Vidal-Carou MC. Diamine oxidase (DAO) supplement reduces headache in episodic migraine patients

 doi:10.20944/preprints202506.1715.v1



with DAO deficiency: A randomized double-blind trial. *Clin Nutr. 2019, 38* (1) 152-158. DOI: 10.1016/j.clnu.2018.01.013

234. Huang Y, Zhang J, You H, Ye F, Yang Y, Zhu C, Jiang YC, Tang ZX. Berberine ameliorates inflammation by inhibiting MrgprB2 receptor-mediated activation of mast cell in mice. *Eur J Pharmacol. 2024, 985*, 177109. DOI: 10.1016/j.ejphar.2024.177109
235. Xiao Y, Cui Y, Zhang Y, Fu W, Liu Y, Liu F. Berberine hydrochloride enhances innate immunity to protect against pathogen infection via p38 MAPK pathway. *Front Immunol. 2025, 16*, 1536143. DOI: 10.3389/fimmu.2025.1536143
236. Gori A, Brindisi G, Daglia M, Giudice MMD, Dinardo G, Di Minno A, Drago L, Indolfi C, Naso M, Trincianti C, Tondina E, Brunese FP, Ullah H, Varricchio A, Ciprandi G, Zicari AM; Nutraceutical and Medical Device Task Force of the Italian Society of Pediatric Allergy, Immunology (SIAIP). Exploring the role of lactoferrin in managing allergic airway diseases among children: unrevealing a potential breakthrough. *Nutrients. 2024, 16* (12), 1906. DOI: 10.3390/nu16121906
237. Gunning L, O'Sullivan M, Boutonnet C, Pedrós-Garrido S, Jacquier JC. Effect of in vitro simulated gastrointestinal digestion on the antibacterial properties of bovine lactoferrin. *J Dairy Res. 2024*, 1-8. DOI: 10.1017/S0022029924000529
238. Dev S, Mizuguchi H, Das AK, Matsushita C, Maeyama K, Umehara H, Ohtoshi T, Kojima J, Nishida K, Takahashi K, Fukui H. Suppression of histamine signaling by probiotic Lac-B: a possible mechanism of its anti-allergic effect. *J Pharmacol Sci. 2008, 107* (2), 159-66. DOI: 10.1254/jphs.08028fp
239. Dong J, Ping L, Cao T, Sun L, Liu D, Wang S, Huo G, Li B. Immunomodulatory effects of the *Bifidobacterium longum* BL-10 on lipopolysaccharide-induced intestinal mucosal immune injury. *Front Immunol. 2022, 13*, 947755. DOI: 10.3389/fimmu.2022.947755
240. Rossignol DA, Frye RE. Cerebral folate deficiency, folate receptor alpha autoantibodies and leucovorin (folinic acid) treatment in autism spectrum disorders: a systematic review and meta-analysis. *J Pers Med. 2021, 11* (11), 1141. DOI: 10.3390/jpm11111141. *Erratum in: J Pers Med. 2022, 12* (5), 721. DOI: 10.3390/jpm12050721
241. Shuid AN, Jayusman PA, Shuid N, Ismail J, Kamal Nor N, Mohamed IN. Association between viral infections and risk of autistic disorder: an overview. *Int J Environ Res Public Health. 2021, 18* (6), 2817. DOI: 10.3390/ijerph18062817
242. Rossignol DA, Genuis SJ, Frye RE. Environmental toxicants and autism spectrum disorders: a systematic review. *Transl Psychiatry. 2014, 4* (2), e360. DOI: 10.1038/tp.2014.4