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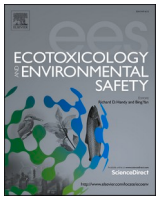

Review

Impact of pesticides exposure during neurodevelopmental period on autism spectrum disorders – A focus on gut microbiota

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ABSTRACT

Accumulating evidence indicates exposure to pesticides during the crucial neurodevelopmental period increases susceptibility to many diseases, including the neurodevelopmental disorder known as autism spectrum disorder (ASD). In the last few years, it has been hypothesized that gut microbiota dysbiosis is strongly implicated in the aetiopathogenesis of ASD. Recently, new studies have suggested that the gut microbiota may be involved in the neurological and behavioural defects caused by pesticides, including ASD symptoms. This review highlights the available evidence from recent animal and human studies on the relationship between pesticides that have the potential to disturb intestinal microbiota homeostasis, and ASD symptoms. The mechanisms through which gut microbiota dysbiosis may trigger ASD-like behaviours induced by pesticides exposure during the neurodevelopmental period via the altered production of bacterial metabolites (short chain fatty acids, lipids, retinol, and amino acid) are also described. According to recent research, gut microbiota dysbiosis may be a major contributor to the symptoms of ASD associated with pesticides exposure. However, to determine the detailed mechanism of action of gut microbiota on pesticide-induced ASD behaviours, actual population exposure scenarios from epidemiological studies should be used as the basis for the appropriate exposure pattern and dosage to be used in animal studies.

1. Introduction

Pesticides in different chemical formulations and concentrations are widely used in agriculture and horticulture for weed and pest control, and they are also used in a public health context to control a wide range of disease vectors and pests affecting the household (Chittrakul et al., 2022; Doğanlar et al., 2018; Li et al., 2014; Pretty and Bharucha, 2015; Tudi et al., 2021). Notably, pesticides residues have been a significant driver of environmental contamination through various routes including air, water, and soil, as only 0.3 % of applied pesticides reach their intended target, while 99.7 % end up somewhere else in the environment. The impact of pesticides exposure on human health is a global concern due to widespread exposure through ingestion, inhalation and skin contact (Jayaraj et al., 2016; Li and Jennings, 2017). Living near pesticide-spraying sites, exposure to pesticides at work and higher body burdens of pesticides have all been linked to neurological damage in adults and children, including an increased risk of Parkinson's disease, cognitive impairment and autism spectrum disorders (ASD) (Temkin et al., 2022). Early life, when the central nervous system (CNS) is still developing, is considered to be the most vulnerable period for exposure to environmental toxins. Early exposure to agricultural pesticides may, either directly or indirectly, affect brain development (Bertoletti et al., 2023; Lyall et al., 2017; Mehri et al., 2021; Roberts et al., 2019). Growing research suggests a connection between pesticides exposure during early life and the development of ASD (Miani et al., 2021; Sagiv et al., 2018; von Ehrenstein et al., 2019).

One of the most frequently identified neurodevelopmental disorders, ASD is characterized by deficits in social interaction and communication, as well as by repetitive, stereotyped behaviours (Chan et al., 2020). ASD has become more common in recent years, but the causes

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underlying this increase are still unknown (Fombonne, 2018). A recent study showed that genetic factors account for 35–40 per cent of ASD cases, while environmental factors, such as prenatal, perinatal, or postnatal exposure to factors such as exposure to synthetic chemicals (e.g., pesticides) may account for 60–65 per cent of the cases. The aetiology of ASD may be predominantly influenced by environmental variables (Pu et al., 2021). Recent studies have highlighted that the development or severity of ASD may be linked to gut microbiota dysbiosis. Dysbiosis of the gut microbiota stimulates bacterial signalling to the brain through humoral, neurological and immune pathways, thereby disrupting the CNS (Zhu et al., 2020). Indeed, exposure to pesticides during early life can disrupt the gut environment and either cause or contribute to a dysbiosis of the microbiota, which can in turn have a negative impact on the CNS (Ayeni et al., 2022; Gama et al., 2022).

In recent years, researchers have drawn attention to the roles that pesticides and gut microbiota dysbiosis play in the aetiopathogenesis of ASD. However, the mechanisms behind these interactions and how they might affect the aetiology of ASD, are not well understood. A few studies have presented evidence that pesticides exposure during early life increases the risk of ASD so far, and this has been linked to aberrant gut microbiota composition (Dong et al., 2020; Perez-Fernandez et al., 2020a; Pu et al., 2020). Here we provide an overview of the evidence from recent studies in animals and humans for a link between pesticides that have the potential to disturb intestinal microbiota homeostasis, and ASD. We further discuss the role of gut microbiota on ASD symptoms linked to pesticides exposure, focusing on signalling mechanisms underlying the interaction between the gut microbiota and the CNS.

2. Methods

In our literature search, we searched the Pubmed database using the following search terms: "pesticides and autism", "autism" and "microbiota", "gut microbiota" and "pesticides" and "neurological dysfunction", as well as "gut microbiota" and "pesticides" and "autism". Only articles published in English were included. After removing duplicates, the eligibility of all the retrieved articles was evaluated based on their titles and abstracts. The authors, with backgrounds in molecular toxicology, neurodevelopmental and neuroendocrinology, child neurology and analytical chemistry, conducted a comprehensive review of the literature obtained from the search. Papers included in this review span the years of 2007 through 2023 and encompass the available literature as of May 2023. In the discussion of the relationship between pesticides and ASD, only those pesticides that have been shown to be associated with ASD in both population studies and animal models were included.

3. Links between pesticides exposure and autism spectrum disorder

3.1. Glyphosate exposure and autism spectrum disorder

The most popular pesticide in the world is glyphosate, an organophosphate herbicide.

(Soares et al., 2021). In addition to its use in non-agricultural areas like water systems, it is utilized to manage weeds in forestry and agriculture (Faria et al., 2021). Since its release on the herbicide market in 1974, it has come to dominate it (Duke, 2018). There was a sharp increase in the use of glyphosate in the mid-1990 s due to the emergence of genetically modified crops that were resistant to it (Marino et al., 2021). Since it has been used more often over the past three decades on crops like corn, soybeans, and wheat, high amounts of glyphosate and its main metabolite, aminomethylphosphonic acid (AMPA), are present at harvest, and there are more glyphosate residues in food (Barnett et al., 2022; Myers et al., 2016). Because glyphosate interferes with the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which is essential for the synthesis of aromatic amino acids in plants but not in animals, the adverse effects of glyphosate on humans have been poorly understood for a long time (Y. Chen et al., 2022; Madani and Carpenter, 2022). However, glyphosate has recently been linked to an increased risk of ASD, celiac disease, leaky gut syndrome, and endocrine disruption (Meftaul et al., 2020).

In a recent population-based case-control research conducted in California, an association between glyphosate use and an elevated incidence of ASD was described. (odd ratio [OR]: 1.16, 95 % CI: 1.06–1.27) (von Ehrenstein et al., 2019). Additionally, a "moderate degree of evidence" has been found for the association between glyphosate and ASD symptoms in children (Ongono et al., 2020). In animal studies, prenatal exposure to glyphosate led to behavioural and oxidative stress abnormalities in rats that were connected with neurodevelopmental issues, with manifestations in the offspring that were consistent with ASD symptomatology (de Oliveira et al., 2022). Specifically, these findings suggest that exposure to glyphosate during gestation and lactation may lead to behavioural problems among male juveniles that have ASD characteristics (Pu et al., 2020, 2021).

3.2. Chlorpyrifos exposure and autism spectrum disorder

Chlorpyrifos (CPF) is an organophosphate pesticide. It has been approved for use on a variety of food crops, including vegetables, fruits, nuts, cotton, cereals, and field crops (Aziz et al., 2021; Bueno and Cunha, 2020; Cutler et al., 2014; Douny et al., 2021; Tong et al., 2021). CPF is also one of the main insecticides used in residential areas (Wang et al., 2016). However, there is overwhelming evidence of its adverse effects on human health, which has led to US rules banning its use in agriculture from 2022 (US EPA, 2022). In spite of this, many nations continue to use this pesticide (Biosca-Brull et al., 2022). The central and peripheral nervous systems are the main target organs for CPF toxicity because its metabolite CPF oxon can inhibit acetylcholinesterase function, which shuts down neurotransmission at cholinergic synapses. Numerous studies have revealed a link between developmental abnormalities and early exposure to CPF (Das et al., 2020; López-Merino et al., 2022; Tu et al., 2022; van Melis et al., 2023). In recent years, increasing concern has been raised about the effect that exposure to CPF during early life could have on the risk of developing ASD.

Studies have already shown an increased incidence of ASD in the offspring following exposure to CPF during pregnancy (OR: 6.10, 95 % CI: 2.4–15.3). Furthermore, the risk of ASD increases as the distance from the residence to the treated field decreases, and with the amount of CPF per kilogram used (Roberts et al., 2007). A prospective cohort study found significant inverse associations between prenatal exposure to CPF and the domain-specific (i.e., communication, gross motor and fine motor) neuropsychological development of children at 12 months (Risk Ratios [RR]: 0.96, 95 %CI: 0.94–0.98) and 18 months (RR: 0.96, 95 %CI: 0.93–0.99) of age (Wei et al., 2023). According to the results of the Childhood Autism Genetic and Environmental Risk (CHARGE) study, children whose mothers were exposed to CPF during the second or third trimester of pregnancy had an increased risk of developing ASD (Shelton et al., 2014). Additionally, a positive association between CPF exposure during pregnancy (defined as use within 2000 m of the family home) and the risk of ASD was found in a 2019 case-control study in California, with an OR of 1.13 for those exposed to CPF (von Ehrenstein et al., 2019). Data from a French longitudinal mother-child cohort showed an increase in autistic traits in 11-year-olds (especially boys) in response to maternal exposure to CPF (incidence rate ratios [IRRs]: 1.39, 95 % CI: 1.07–1.82) (Lizé et al., 2022). In animal models, exposure to CPF in early life was shown to affect behaviours in a dose-dependent manner characterized by neurodevelopmental disorder (NDD) phcenotype (e.g., deficits in social communication, and repetitive, restrictive behaviours) (López-Merino et al., 2022; Berg et al., 2020; Perez-Fernandez et al., 2020a; Lan et al., 2017). In addition, males are more vulnerable to prenatal exposure to CPF, which is consistent with the sex difference observed in the prevalence of ASD (Biosca-Brull et al., 2022). However, a recent study found that prenatal exposure to CPF affects social

behaviour in a sex-dependent manner, with impaired social novelty preference in female mice transgenic for apolipoprotein E3 and E4. The apparent discrepancy in the sex of the affected individuals may be due to differences in the time of exposure during neurodevelopment (prenatal or postnatal) and to different genetic backgrounds (Biosca-Brull et al., 2023). In addition, mice belonging to the inbred strain BTBR T + tf/J (BTBR mice) exposed to CPF during prenatal development showed more severe autistic-like behavioural features, such as limitations in the social and communicative domains, expressed as changes in the emission of ultrasonic vocalizations (USVs), and increased repetitive activities (De Felice et al., 2015). Prenatal exposure of rats to CPF leads to reduced USVs on postnatal day 7, suggesting communication difficulties similar to those of ASD (Morales-Navas et al., 2020). In particular, a cumulative effect on CNS damage leading to a more severe ASD-like phenotype may occur in animals with genetic susceptibility subjected to prenatal exposure to CPF (Perez-Fernandez et al., 2022).

3.3. Pyrethroids exposure and autism spectrum disorder

A new generation of insecticides, including pyrethroids, that are effective in the control of a wide range of pests and have a highly selective toxicity have been created to replace previously used categories of insecticides such as organophosphates, organochlorines and carbamate (H. Li et al., 2017). Exposure to pyrethroids is common as a result of occupational and non-occupational activities, and their metabolites have been discovered in the bodily fluids of American military staff, and agricultural workers. Pyrethroids residues have also been found in a number of food items, including cereals, fruits, vegetables, and dairy products in Brazil, Colombia, India, and Spain, as well as in breast milk samples from lactating women in those areas. Pyrethroids can also be absorbed through the skin, as they are present in numerous household products such as shampoo, detergent, and anti-mosquito wipes (Glorennec et al., 2017; Ravula and Yenugu, 2021). Therefore, regardless of whether the affected population has used the pesticides directly or not, there is enough epidemiological evidence to suggest that pyrethroids exposure is prevalent globally. Numerous studies have connected pyrethroids to a variety of neurological symptoms, and more recent research has revealed that pyrethroids exposure in utero or during infancy may be linked to neurobehavioural problems in children (e.g., ASD) (Furlong et al., 2017).

According to data from the Childhood Autism Risks from Genetics and Environment (CHARGE) study, pyrethroids exposure during the third-trimester of pregnancy was associated with a higher incidence of ASD in California (Shelton et al., 2014). One study found that pregnant women with a slightly higher urinary levels of the main pyrethroid metabolite (3-phenoxybenzoic acid, 3-PBA) had also a slightly higher risk of having a child with ASD symptoms (relative risk ratio [RRR]: 1.50, 95 % CI: 0.89–2.51) (Barkoski et al., 2021). Another study in California found a weak positive association between prenatal exposure to cypermethrin (another type I pyrethroid used in agriculture) and ASD (OR: 1.10, 95 % CI: 1.01–1.20) (von Ehrenstein et al., 2019). In animal models, long-term exposure to pyrethroids in zebrafish can reduce their social interactions, a typical ASD-like symptom (Tamagno et al., 2023). In addition, pyrethroids exposure during prenatal development and the first few months after birth enhanced the risk of ASD in a Chd8 haploid mice model (Jiménez et al., 2022).

3.4. Imidacloprid exposure and autism spectrum disorder

Imidacloprid, also known as IMI, is a colourless neonicotinoid insecticide belonging to the chloronitroguanidine compound class. 1-((6-chloro-3-pyridinyl) methyl)-N-nitro-2-imidazolidnimine is the chemical name of imidacloprid. It has many household uses, including control of cockroaches, termites, fleas (in pets) and garden pests (Pang et al., 2020). Most of the active component of neonicotinoids is absorbed by the soil and enters water bodies through runoff, storms, and jet streams, only a small percentage of it is actually taken up by plants after application. Residues have been discovered in a wide range of environments and in different foods items worldwide, including drinking water, indicating that humans may be exposed to imidacloprid through a wide variety of potential routes (López-Gálvez et al., 2020; Luo et al., 2021; Wang et al., 2020). Despite the relatively low toxicity of neonicotinoid pesticides to mammals, there is growing evidence that their widespread use may have adverse effects on organisms other than their intended targets. It has been discovered that imidacloprid changes the density of neuroreceptor subtypes, which could have effects on the pathogenesis of ASD (Cimino et al., 2017). In a case-control study, mothers of children with ASD were found to be twice as likely to have been exposed to imidacloprid compared to other mothers. The findings indicated a 30 % higher prevalence of ASD in the offspring of pregnant women exposed to imidacloprid (Keil et al., 2014). ASD-like behavioural characteristics in rodent models have been linked to imidacloprid exposure, with "high levels of evidence" supporting changes in behavioural characteristics, learning, and memory abilities (Ongono et al., 2020). In addition, imidacloprid exposure induced behavioural impairments in drosophila associated with neurochemical changes similar to those observed in neurodevelopmental disorders such as ASD and ADHD (as illustrated in Table 1) (Janner et al., 2021; Kim et al., 2017).

4. Role of the gut microbiota in the neurological dysfunction caused by pesticide exposure

The involvement of the gut microbiota in pesticide-induced toxicity to non-target organisms is receiving increasing attention based on recently advanced evidence suggesting that the gut microbiota can be altered in response to many environmental contaminants, including some pesticides. These imbalances in the microbiota may be detrimental to consumer health (Li et al., 2022; Liang et al., 2019; Mao et al., 2018; Ueyama et al., 2022). Indeed, emerging evidence supports the hypothesis that exposure to environmental pesticides may alter the composition of the gut microbiome, along with pathological alterations in the CNS (Mao et al., 2018).

By altering the gut microbiota, exposure to pesticides has been shown in numerous studies to alter brain function, which may be associated with pesticide-induced neurologic disorders (Table 2). Although glyphosate targets (the shikimate pathway) are absent from human cells, the shikimate pathway is crucial for maintaining the ecological balance of the gut microbiota. Disruption of the shikimate pathway in human gut microbes may affect the nervous system (Rueda-Ruzafa et al., 2019). Recently, it has been shown that children whose mothers had been exposed to glyphosate present a disrupted gut microbiota. The abundance of *Clostridium sp. Clone-1*, *-46*, *Butyricimonas virosa*, and *Proteobacteria* is increased, while that of *Eubacterium plexicaudatum*, *Lachnospiraceae bacterium 538*, *Clostridium tertium*, and *Bacteroideta* is reduced. These changes in the microbiome are involved in the activation of phagocytic cells and are accompanied by cognitive and social interaction deficit as well as repetitive stereotyped behaviours (Del Castilo et al., 2022; Pu et al., 2020). In juvenile common carps, glyphosate exposure led to a decrease in the abundance of *Cetobacterium* and an increase in that of *Mycobacterium*, *Microbacterium*, and *Nakamurella*. This imbalance may have been directly responsible for the observed changes in motility and growth inhibition in the carps, since it decreased the permeability of the blood-brain barrier and disrupted acetylcholinesterase function (J. Chen et al., 2022). In addition to its effects on the offspring, glyphosate exposure has been found to affect maternal behaviour in rats, and may lead to changes in neuronal plasticity. There was a decrease in the abundance of some bacterial species, including *Lachnospiraceae*, *Butyricicoccus*, and *Ruminococcaceae UCG-013*, while others such as *Turicibacter* and *Alloprevotella* became more abundant instead (Dechartres et al., 2019). Another similar non-selective herbicide, glufosinate ammonium, has also been shown to alter the composition of the microflora, down-regulating *Firmicutes* and upregulating

Table 1
Evidence of association between pesticides exposure and autism spectrum disorder (ASD).

Pesticides	Study design	Results	Reference
Glyphosate	Case-control study	When glyphosate herbicides are used during pregnancy within 2000 m of the family home, the risk of ASD in the offspring is increased (OR: 1.16, 95 % CI: 1.06–1.27)	von Ehrenstein et al. (2019)
	Rats	Perinatal exposure to glyphosate induced behavioural changes in the offspring that was consistent with symptoms of ASD.	de Oliveira et al. (2022)
	ddY mice	ASD-like behavioural abnormalities may occur in male offspring following exposure to glyphosate during prenatal development and lactation.	Pu et al., (2020, 2021)
Chlorpyrifos	Case-control study	Exposure to chlorpyrifos in mothers was positively correlated with ASD in the offspring (OR: 6.10, 95 % CI: 2.4–15.3).	Roberts et al. (2007)
	Cohort study	A significant inverse association between prenatal exposure to chlorpyrifos and domain-specific neuropsychological development in children at 12 months (RR: 0.96, 95 % CI: 0.94–0.98) and 18 months (RR: 0.96, 95 % CI: 0.93–0.99) of age was identified.	Wei et al. (2023)
	Cohort study	An increase in autistic traits in 11-year-olds has been linked to prenatal exposure to chlorpyrifos (IRRs: 1.39, 95 % CI: 1.07–1.82)	Lizé et al. (2022)
	Case-control study	There was an increased risk of ASD in offspring exposed to chlorpyrifos during the second or third trimester of prenatal development (OR: 2.0, 95 % CI: 1.1–3.6).	Shelton et al. (2014)
	Case-control study	There was a positive association between exposure to chlorpyrifos during prenatal development and the risk of ASD. (OR: 1.13, 95 % CI: 1.05–1.23).	von Ehrenstein et al. (2019)
	Sprague-Dawley rats	Exposure to CPF during development impairs behaviours that are typical of the ASD phenotypes (impaired social communication, and confined, repetitive conduct).	Berg et al. (2020)
	BTBR mice	Exposure to CPF during prenatal development led to several behavioural traits typical of ASD, including impairments in the social and communication domains (alterations in ultrasonic vocalization, and high levels of repetitive behaviours).	De Felice et al. (2015)
	Wistar rats	Reduced ultrasonic vocalizations on postnatal day seven in pups prenatally exposed to CPF, suggesting ASD-like communication deficits.	Morales-Navas et al. (2020)
	C57BL/6 mice	Exposure to CPF during prenatal development had negative long-term effects on social behaviour and decreased exploration of unfamiliar items.	Lan et al. (2017)
	C57BL/6 mice	Social behaviour and excitatory-inhibitory balance were affected by prenatal exposure to CPF in a sex-dependent manner.	Biosca-Brull et al. (2023)
	fmr1-KO rats	An exacerbation of the ASD-like phenotype was noticed in response to CPF exposure during prenatal development.	Perez-Fernandez et al. (2022)
Pyrethroids	Case-control study	Exposure to pyrethroids in the third trimester of prenatal development was associated with increased odds of ASD symptoms (OR: 1.87, 95 % CI: 1.02–3.43).	Shelton et al. (2014)
	Cross-sectional study	Mildly higher urinary levels of 3-phenoxybenzoic acid, a key metabolite of pyrethroids, in pregnant women were associated with a small increase in the risk of ASD in their offspring.	Barkoski et al. (2021)
	Case-control study	Prenatal exposure to methrin (a type I pyrethroid) was linked to a significantly higher risk of ASD (OR: 1.10, 95 % CI: 1.01–1.20).	von Ehrenstein et al. (2019)
	Zebrafish	Long-term exposure to pyrethroids reduced social interactions, as observed in ASD.	Tamagno et al. (2023)
	Chd8V986 */+ mice	Prenatal and early postnatal exposure to pyrethroids increased the risk of ASD.	Jiménez et al. (2022)
Imidacloprid	Case-control study	Women exposed to imidacloprid at home during pregnancy had a 30 % increased risk of ASD in their offspring.	Keil et al. (2014)
	Drosophila melanogaster	Exposure to imidacloprid induced autism-like phenotypes.	Janner et al. (2021)

Bacteroidetes, and this was linked to disruptions in locomotor activity, ASD-like behaviours, and short-term memory impairments in mice (Dong et al., 2020).

Similar to glyphosate, the broad-spectrum organophosphate insecticide CPF has also been demonstrated to harm the nervous system by disrupting the gut microbiota. A study showed that long-term exposure to CPF increased the spontaneous vertical activity of mice after acute stress, decreased the sensitivity of the cholinergic system, increased the sensitivity of the GABAergic system, and upregulated the muscarinic 2 receptor and GABA-A-α2 receptor subunits in the dorsal striatum and frontal cortex, respectively. These effects were associated with the dysregulation of the gut microbiome, including the increased abundance of *Anaerobranca zavarzinii* and the decreased abundance of *Alkalaceticum*, *Nitrincola*, and *Lacisaponensis*, among others (Perez-Fernandez et al., 2020b). Another study in rats showed that CPF can disrupt the gut microbiome, leading to dysfunction of the

Table 2
Changes in cerebral function induced by pesticides exposure are accompanied by microbiome alterations.

pesticides	models	Changes in microbiome	Cerebral function effects	Reference
Glyphosate	ddY mice	↓ *Eubacterium plexicaudatum* ↓ *Lachnospiraceae bacterium 538* ↓ *Clostridium tertium* ↑ *Enterorhabdus muris* ↑ *Clostridium sp. Clone-1* ↑ *Clostridium sp. Clone-46* ↑ *Butyricimonas virosa*	Cognitive deficits Social interaction deficit	Pu et al. (2020)
	Sprague-Dawley rats	↓ *Lachnospiraceae* ↓ *Butyricicoccus* ↓ *Ruminococcaceae UCG-013* ↑ *Turicibacter* ↑ *Alloprevotella*	Changes in maternal behaviours and neuronal plasticity	Dechartes et al. (2019)
	Swiss mice	↓ *Bacteroideta* ↑ *Proteobacteria* ↑ *Desulfobacteria*	Social interaction deficit Repetitive stereotyped behaviour Morphological changes in brain-resident glial cells	Castilo et al. (2022)
	Juvenile common carps	↓ *Cetobacterium* ↑ *Mycobacterium* ↑ *Microbacterium* ↑ *norank_f_JG30_KF_CM45* ↑ *Nakamurella*	Reduction in blood-brain barrier permeability Disruption of acetylcholinesterase activity Reduction in the swimming distance of larvae	J. Chen et al., 2022
Chlorpyrifos	Wistar rats	↓ *Alkalaceticum* ↓ *Nitrincola* ↓ *Lacisaponensis* ↓ *Vorgesella Perlucida* ↑ *Anaerobranca zavarzinii*	Hypermobility and stress-related hypermobility Hypo- or hyper-sensitization of the cholinergic and GABAergic systems Increased transcription of the GABA-A-A2 subunit and M2 receptor genes	Perez-Fernandez et al. (2020b)
	Wistar rats	↓ *Romboutsia Turicibacter* ↓ *Clostridium sensu stricto 1* ↑ *Streptococcus* ↑ *Ruminiclostridium* ↑ *norank_f_Coriobacteriaceae*	Inhibition of acetylcholinesterase activity Stimulation of pituitary hormones release Systemic inflammation (TNF-α, etc.)	Li et al. (2019)
	Wistar rats	↓ *Caldicellulosiruptor* ↓ *Rodhosphirillum* ↓ *Mycoplasma* ↓ *Helicobacter* ↓ *Methylobacterium* ↓ *Neorickettsia* ↓ *Thiomonas* ↓ *Ehrlichia* ↓ *Rhodobacter* ↓ *Saccaropolyspora* ↓ *Chlorobaculum* ↓ *Chondromyces* ↓ *Leptothrix* ↑ *Slackia* ↑ *Aggregatibacter* ↑ *Carboxydocella*	Reduced responsiveness to social novelty in adults	Perez-Fernandez et al. (2020a)
	C57BL/6 mice apoE-TR mice	↓ *Streptococcus* ↑ *Rhodothermus* ↑ *Helicobacter* ↓ *Prevatella* ↓ *Lachnospiraceae*	Changes in cerebral short-chain fatty acid levels	Guardia-Escote et al. (2020)
Pyrethroids	Wistar rats	↓ *Blautia* ↑ *S24–7* ↑ *Ruminococcaceae*	Loss of dopaminergic neurons from Substantia nigra	Bordoni et al. (2019)

(*continued on next page*)

Table 2 (*continued*)

pesticides	models	Changes in microbiome	Cerebral function effects	Reference
	C57BL/6 mice	↓ *Lactobacillus* ↓ *Bifidobacterium*	Neuronal inflammation	Seth et al. (2019)
Imidacloprid	P. clarkii	↓ *Aeromonas* ↓ *Acinetobacter* ↑ *Tenericutes* ↑ *Cronobacter* ↑ *Shewanella*	Motor dysfunction Acetylcholinesterase inhibition oxidative stress	Huang et al. (2021)
Diazinon	C57BL/6 mice	↓ *Butyrivibrio* ↓ *Shuttleworthia* ↓ *Staphylococcus* ↓ *Johnsonella*	Neurotransmitter downregulation	Gao et al. (2017)
Glufosinate ammonium	ICR mice	↓ *Firmicutes* ↑ *Bacteroidetes*	Damaged locomotor activity ASD-like behaviours Impaired short-term memory formation	Dong et al. (2020)

hypothalamic-pituitary-adrenal axis and causing inflammation by decreasing the abundance of *Romboutsia*, *Turicibacter*, *Clostridium sensu stricto 1* , among others (Li et al., 2019). In addition, a study investigated the effects of medium and long-term low-dose exposure to CPF on socialization and intestinal microbiota composition in rats, with the results showing reduced responsiveness to social novelty in the adults, along with a decrease in the abundance of some bacterial species, including *Caldicellulosiruptor*, *Rodhosphirillum*, and *Mycoplasma*, and an increase in *Leptothrix*, *Slackia,* and *Aggregatibacter*, among others (Perez-Fernandez et al., 2020a). The levels of short-chain fatty acids (SCFAs) in the brain, which play a role in the regulation of several cerebral functions, were also impacted by exposure to CPF during early childhood. These alterations might be associated with changes in the abundance of *Streptococcus*, *Rhodothermus*, and *Helicobacter*, among others (Guardia-Escote et al., 2020). Another widely used organophosphate broad-spectrum insecticide, diazinon, has been shown to induce neurotransmitter dysregulation in mice by decreasing the abundance of some bacteria such as *Butyrivibrio* and *Shuttleworthia* (Gao et al., 2017).

Parkinson's disease has been associated to pyrethroids exposure, as pyrethroids have been shown to trigger the loss of dopaminergic neurons from the substantia nigra in Wistar rats, accompanied by a decrease in the abundance of *Blautia* and an increase in the abundance of *Ruminococcaceae* (Bordoni et al., 2019). Furthermore, in a rodent model for Gulf War Illness (GWI), dysbiosis of the gut microbiota was found. This dysbiosis, caused by chemicals used during the conflict (permethrin and pyridostigmine bromide), was positively associated with neuroinflammation. In particular, the reduction in epithelial tight junction protein and the neuroinflammation were improved after antibiotic treatment (Seth et al., 2019). In the Procambarusclarkii (P. clarkia) model, imidacloprid was postulated to induce neurotoxicity and locomotor impairment associated with an increase in pathogenic genera and a decrease in beneficial bacterial communities (Huang et al., 2021).

5. Possible mechanisms for gut microbiota involvement in the pathogenesis of autism spectrum disorders

The regulation of the neuroendocrine, neuroimmune and central nervous systems is critically influenced by the gut microbiota. As a result, it is possible to control the interaction between the gut and the nervous system (Chernikova et al., 2021; Sivamaruthi et al., 2020). A growing body of research shows that gut microbial dysbiosis contributes to the pathogenesis of a wide range of illnesses, including celiac disease (CD), allergies, inflammatory bowel syndrome (IBS), asthma, cardiovascular disease, metabolic syndrome, and obesity. Dysbiosis has also been linked to neurological diseases, including ASD, Alzheimer's disease, multiple sclerosis, Parkinson's disease, and stroke (Cryan et al., 2020; Taniya et al., 2022). Gastrointestinal (GI) issues are among the most prevalent comorbidities of these diseases, 46–84 % of people with ASD report experiencing gastrointestinal symptoms, including lower (i.e., constipation and diarrhoea) and upper GI symptoms (i.e., nausea and vomiting, stomach aches, and pain) (Adams et al., 2011; Al-Beltagi, 2021; Ferguson et al., 2019; Saurman et al., 2020). The possibility that gut microbiota may be involved in the gastrointestinal pathophysiology of ASD is suggested by the prevalence of GI symptoms in autistic individuals (Strati et al., 2017). Meanwhile, a recent analysis raises the possibility that gut microorganisms may be crucial in social behaviour disorders, one of the typical symptoms of ASD (Cowan et al., 2020). Compared to neurotypical children, those with ASD show dysbiosis regarding some specific gut microbiota species. The severity of autistic symptoms and associated GI problems have been linked to changes in the gut microbiota (Iglesias-Vázquez et al., 2020). Intestinal and neurobehavioural dysfunction in ASD may be caused by disruptions in the system underpinning the gut-brain axis, particularly the disrupted gut microbiota (Yang et al., 2020).

Intestinal hormones, neuroactive substances, and products and metabolites derived from various intestinal microbiota regulate the

function of the CNS through the enteric nervous system (ENS), vagal nerve, circulatory system, or immune system pathways (Liu et al., 2022). Intestinal serotonin (5-hydroxytryptamine, 5-HT), located in enterocytes, is the best characterized intestinal hormone and has multiple functional receptors in the nervous system, which is critical for ENS and CNS development. Over 25 % of ASD children had increased levels of 5-HT in their bloodstream according to epidemiological studies, suggesting a link between 5-HT and ASD (Muller et al., 2016). Recent studies have found that elevated levels of 5-HT in some children with ASD may be due to a deficiency in *Bacteroides spp* (Dan et al., 2020). Of the possible pathways linking the gut microbiota to the brain, the vagus nerve is the most direct. The scaffolding protein encoded by the Shank3 gene is located in synapses. This gene has been linked to ASD symptoms in humans, and to ASD-like behaviours in animal models. Compared to wild type mice, mice in which this gene has been disrupted exhibit intestinal dysbiosis. Notably, exogenous administration of *L. reuteri* to mice with the Shank3b mutation improves deficiencies in social behaviour, social novelty preference, and brain plasticity via the activation of the vagus nerve and the hypothalamic oxytocin system (Sgritta et al., 2019). Intestinal dysbiosis, which is characterized by an unbalanced population of both beneficial and pathogenic bacteria in the gut, affects children with ASD. The pathogenic bacteria produce compounds such lipopolysaccharides and opioid peptides that enter the bloodstream and cause inflammation and damage to nerve tissue, compromising the integrity of the intestinal barrier. These dangerous metabolites also disrupt neurotransmitter function in the brain, causing abnormal behavioural patterns such as reduced social interaction and inappropriate language (Sivamaruthi et al., 2020).

The importance of microbiota-derived metabolites and their cellular and molecular constituents to human physiology is becoming more widely acknowledged. These substances significantly affect the homeostasis of the host organism (Mao et al., 2018). Metabolomic alterations have been linked to the origin and/or persistence of behavioural impairments associated with ASD, according to research by Hsiao et al. (Hsiao et al., 2013). Numerous metabolites produced by the gut microbiota have an impact on brain function, either directly or indirectly. If the gut microbiome changes, this might potentially affect how metabolites are produced, which would in turn affect the variety and availability of nutrients and microbial metabolites (Nagpal et al., 2019; Sharon et al., 2019; Wong et al., 2021). In general, important host metabolic, immune, and neurologic activities in ASD are regulated by microbiological by-products, including bile acids, SCFAs, and the tryptophan metabolites kynurenic and quinolinic acid (Gama et al., 2022). According to previous research, metabolite imbalance in the faeces of autistic individuals and animal models may be connected to both gastrointestinal issues and behavioural signs of ASD (De Angelis et al., 2013; Kang et al., 2018). For example, the levels of acetate, propionate, and valerate, known to have a beneficial impact on peripheral and central nerves and to ameliorate the behavioural, neuropathological, and metabolic alterations identified in children with autism, were considerably lower in these children (−27 %, $P = 0.00002$) (Wang et al., 2012; Adams et al., 2011; Nagpal et al., 2019). However, children with ASD had higher levels of SCFAs and ammonia in their faeces, according to Wang et al. (Wang et al., 2012). This discrepancy may be due to natural variations in the gut microbiota of different populations, as well as to technical variations in sample preparation between studies (Liu et al., 2019). Li et al. suggested that metabolites derived from the gut microbiota, such as SCFAs, may influence ASD-like behaviours through the vagal pathway (Q. Li et al., 2017). Furthermore, studies in germ-free (GF) mice have shown that SCFAs can change the permeability of the blood brain barrier, which in turn affects the level of exposure of brain tissue to beneficial or harmful compounds in the circulation, thereby affecting neuroinflammation or neurosynaptic activity (Tran and Mohajeri, 2021).

Changes in the levels of some other metabolites, such as amino acids synthesized by the gut microbiota, have also been involved in the pathophysiology of ASD. Tyrosine, phenylalanine, and tryptophan are three aromatic amino acids that humans are unable to synthesize and must obtain from either their food or their gut microbiota in order to meet their nutritional needs. All three aromatic amino acids can be synthesized by gut microbiota using the shikimate route. It can therefore be hypothesized that the gut microbiota regulates the pool and composition of amino acids available to the host (Tran and Mohajeri, 2021). The small aromatic metabolite p-cresol is derived from tyrosine fermentation by several species from the gut microbiota (e.g. *Bacteroidaceae*, *Clostridiaceae*, *Oscillospira*, *Coriobacteriaceae*, *Ruminococcus*, *Christensellaceae*, *Mogibacteriaceae*, *Akkermansia*, and *Clostridiales*) and is consistently observed at elevated levels in faecal samples from ASD patients (Kang et al., 2018; Needham et al., 2021). Indeed, recent studies confirmed that the microbial metabolite p-cresol specifically evokes core behavioural symptoms of ASD in mice. Notably, social behavioural deficits induced by p-cresol appear to be dependent on the microbiota (Bermudez-Martin et al., 2021). In addition, a link between anomalies in tryptophan metabolism and dysbiosis of the intestinal bacterial microbiota was identified in children with ASD. Several bacteria belonging to the genera *Clostridium*, *Ruminobacter*, *Braunschweiger* and *Lactobacillus* have been identified as being involved in tryptophan metabolism. Studies in animal models have also shown that tryptophan-related metabolites in ASD correlate with the behaviours of mice transplanted with faeces from children with ASD, which show similar symptoms (Xiao et al., 2021). By activating receptors distributed along the vagus nerve, intestinal glutamates significantly enhance the two-way exchange of information between the brain and the gut. A disruption in the glutamatergic neurotransmitter system of the gut has been identified in studies focusing on the gut microbiota in ASD, and this may contribute to the onset of ASD symptoms (Montanari et al., 2022). Recent evidence suggests that disturbances in glutamate metabolism in children with ASD are linked to changes in the abundance of 2-ketoglutamate, and with changes in the abundance of gut microbiota species linked with glutamate metabolism, including a decrease in *Bacillus vulgaris* and an increase in *Eggerthella lenta* and *Clostridium botulinum* in faecal samples (Wang et al., 2019). Altered amino acid metabolism regulated by intestinal microbiota may sometimes be corrected by supplementation of prebiotics, probiotics, amino acids, and their derivatives, which may become a potential novel strategy for the treatment of ASD symptoms (Zhu et al., 2022).

6. Possible mechanisms of autistic-like behaviours induced by pesticides exposure: involvement of dysbiosis

Due to certain contributions of pesticides-induced dysbiosis, concerns have been raised about their possible role in connecting pesticides exposure with the pathogenesis of ASD. Several recent reports have revealed possible mediating mechanisms between pesticides exposure and the onset of ASD (Fig. 1) (Del Castilo et al., 2022; Dong et al., 2020; Perez-Fernandez et al., 2020b; Pu et al., 2020). Data from ddY mice showed that exposure to 0.098 % glyphosate during pregnancy and lactation resulted in ASD-like behavioural changes associated with gut microbial dysbiosis and SCFAs in faecal samples, decreased levels of N-methyl-D-aspartate receptor (NMDAR)-associated amino acids (e.g, GABA, D-serine, glutamine, glutamate, glycine, L-serine) in blood and brain, and increased soluble epoxide hydrolase activity in the hippocampus, prefrontal cortex, and striatum of young offspring. This work suggests that enhanced soluble epoxide hydrolase activity may be a factor in the behavioural impairments resembling ASD observed in children after glyphosate exposure (Pu et al., 2020). Notably, the soluble epoxide hydrolase deficiencies in eicosanoid metabolism are linked to maternal immune activation and to behavioural disorders that resemble ASD (Ma et al., 2019). In another in-vivo study by Del Castilo, mice exposed to low doses of RoundUp® (0.075 % w/v), a glyphosate-based herbicide, over an extended period of time (from conception to adulthood) had abnormal social behaviours and an increase in repetitive

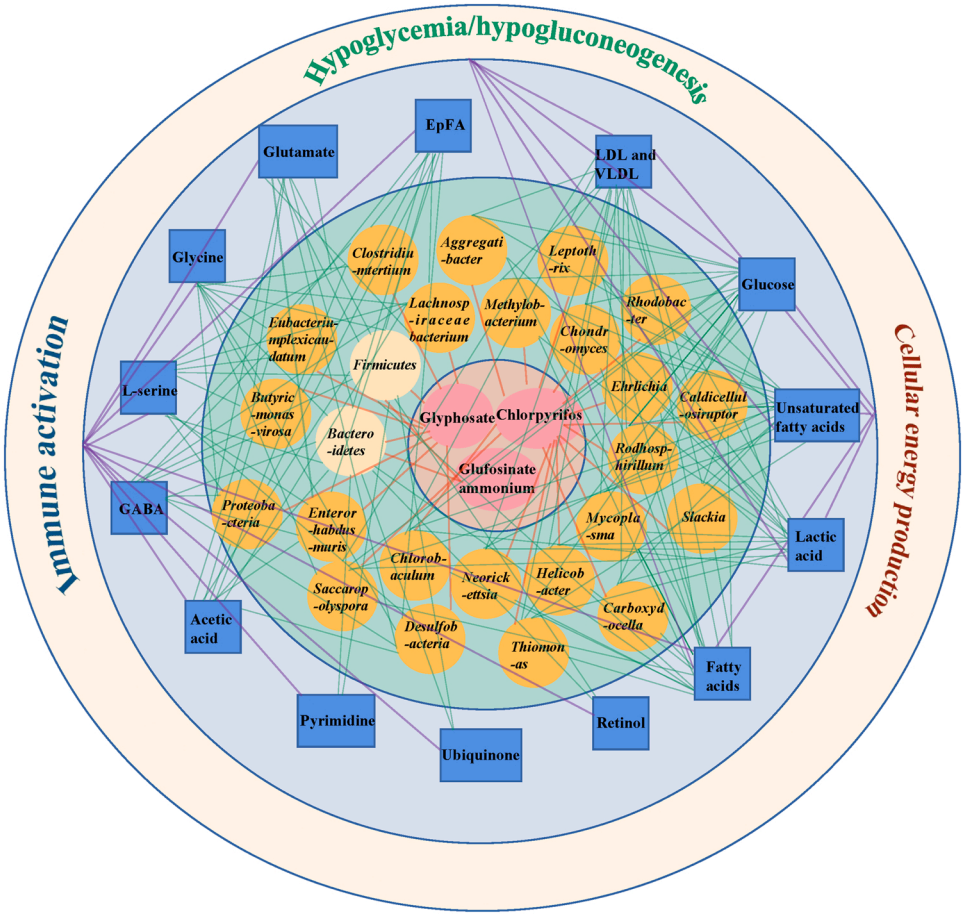

Fig. 1. Mechanisms of ASD-like behaviours induced by exposure to pesticides and involving the disruption of gut microbiota, according to the available direct evidence. The innermost circles indicate pesticides. Those within the green area represent the altered gut microbiota resulting from exposure to these pesticides, with the lighter circles representing altered microbiota at phylum level and the darker ones representing altered microbiota at genus level. The squares indicate altered metabolites resulting from changes in the gut microbiota. The outer layer indicates the mechanisms by which pesticides have been postulated to cause ASD-like behaviours via the disruption of the gut microbiota and its associated metabolites. GABA, Gamma-aminobutyric acid; EpFA, Epoxy fatty acid; LDL, Low-density lipoprotein; VLDL, Very low-density lipoprotein.

activity, but no alterations in learning or memory function. Activation of phagocytic cells in cortical brain tissue and increased permeability of the intestinal barrier were found, accompanied by changes in the composition of the gut microbiome in these mice (Del Castilo et al., 2022). Chronic exposure to glufosinate ammonium (an alternative to paraquat) during early childhood has been linked to ASD-like behaviours. These aberrant behaviours are mostly linked to disruptions in the gut microbiota and microbiome-related retinol metabolism, suggesting that dysbiosis may directly cause pesticide-related abnormal behaviours resembling ASD. Even more concerning, pesticide-induced damage to the CNS and neurobehavioural changes at crucial stages of neurodevelopment may be irreversible or incurable (Dong et al., 2020). Observations in a rat model exposed to low CPF dosages during the late postnatal period and pre-weaning developmental stages showed a significant decrease in response to social novelty, along with significant gut microbiome dysbiosis, hyperlipidemia (elevated plasma levels of saturated and unsaturated fatty acids, and very low-density lipoproteins), a hypoglycemia/hypogluconeogenesis profile (decreased plasma glucose levels), and altered amino acid profile in females (Perez-Fernandez et al., 2020a). Similar to this, lipid and amino acid metabolic abnormalities in plasma and faecal samples have been linked to ASD symptoms (Needham et al., 2021). Although these studies explored potential mechanisms and supported the key role of gut microbiota dysbiosis in pesticide-induced ASD-like behaviours, they fall far short of establishing exactly how the gut microbiota and the host CNS interact with each other after exposure to pesticides. Further research should be performed to determine the role that specific bacterial species play in this phenomenon.

7. Future direction and conclusions

Although several studies have indentified potential pathways by which dysbiosis of the gut microbiota may be directly involved in triggering pesticide-induced ASD-like behaviours (including alterations in SCFAs, lipids, retinol, and amino acids derived from gut microbiota metabolism, Fig. 2), further studies are warranted to identify the role of specific intestinal bacterial strains and their mechanisms of action. The available evidence linking changes in the gut microbiota and ASD-like behaviours associated to pesticides exposure is primarily derived from animal models, and that from epidemiological studies is limited. In addition, these animal model studies were conducted using much higher pesticides concentration than those which humans are normally exposed to, suggesting that these data may not be directly applicable to humans. Furthermore, current research has focused on exploring the mechanisms by which exposure to a single pesticide can lead to gut microbiota dysbiosis and to the associated ASD-like behaviours, but evidence from epidemiological studies confirming pesticides exposure as a potential cause of ASD suggests that the most relevant scenario is that of combined exposure to multiple pesticides. Therefore, future case-control or cohort studies should focus on gut microbiome homeostasis in ASD patients in relation to pesticides exposure, to provide direct evidence on whether pesticides affect ASD-like behaviours via gut microbiome dysbiosis. Furthermore, to ascertain the precise mechanisms of action of specific bacterial strains in the gut and their role in eliciting ASD-like behaviours following pesticides exposure, investigations based on actual exposure patterns and dosages obtained from epidemiological studies are essential.

In conclusion, significant progress has been made in the exploration of the relationship between the gut microbiome and ASD, and this has

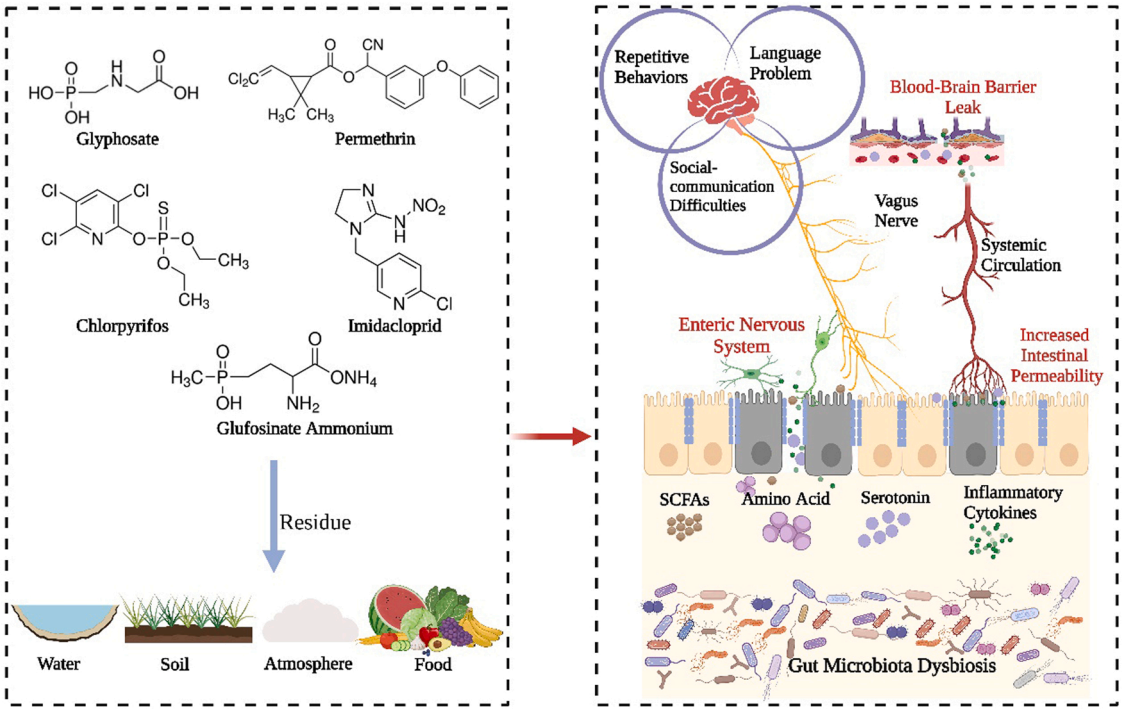

Fig. 2. Schematic illustration of the potential pathways through which exposure to commonly used pesticides may cause disruption of the gut microbiota and results in the development of ASD-like behaviours. Pesticides residues in the water, soil, air, and food can lead to a dysbiotic gut microbiome, which is characterized by abnormalities in associated metabolites such as inflammatory cytokines, amino acids, or short-chain fatty acids (SCFAs). Some of the elements used to create the images are derived from BioRender.com.

provided substantial evidence on the role of the gut microbiome in the aetiology and pathophysiology of ASD. Recent studies have suggested that exposure to some pesticides, especially during the sensitive neurodevelopmental period (early in life), may result in dysbiosis of the gut microbiota, which is in turn an important contributor to neurological defects and behavioural impairments. This article reviews the evidence available so far related to pesticides exposure during early life and its relevance to elucidate the aetiology of ASD, highlighting the importance of disruption to the gut microbiome in this process. We also emphasize that gut microbiota dysbiosis is a crucial factor in ASD symptoms linked to pesticides exposure, which has obvious relevance for the development of novel treatments and preventive measures targeting the appropriate biological underpinnings.

Conflicts of interest

The authors declare no conflict of interest.

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Authors contribution

Conceptualization, M.Y., Y.Y.; validation, Y.Y., Y.X., G.Y.; writing—original draft preparation, Y.Y., S.Z.; writing—review and editing, M.Y., G.Y., S.Z.; supervision, M.Y., G.Y.; funding acquisition, M.Y.; All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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